Published in final edited form as:

J Perinatol. 2017 August ; 37(8): 947–952. doi:10.1038/jp.2017.62.

Impact of brain injury on functional measures of amplitude-integrated EEG at term equivalent age in premature infants

NM El Ters¹, ZA Vesoulis¹, SM Liao¹, CD Smyser², and AM Mathur¹

¹Division of Newborn Medicine, Department of Pediatrics, Washington University School of Medicine, St Louis, MO, USA

²Division of Pediatric Neurology, Washington University School of Medicine, St Louis, MO, USA

Abstract

OBJECTIVE—To evaluate the association between qualitative and quantitative amplitude-integrated EEG (aEEG) measures at term equivalent age (TEA) and brain injury on magnetic resonance imaging (MRI) in preterm infants.

STUDY DESIGN—A cohort of premature infants born at < 30 weeks of gestation and with moderate-to-severe MRI injury on a TEA MRI scan was identified. A contemporaneous group of gestational age-matched control infants also born at < 30 weeks of gestation with none/mild injury on MRI was also recruited. Quantitative aEEG measures, including maximum and minimum amplitudes, bandwidth span and spectral edge frequency (SEF₉₀), were calculated using an offline software package. The aEEG recordings were qualitatively scored using the Burdjalov system. MRI scans, performed on the same day as aEEG, occurred at a mean postmenstrual age of 38.0 (range 37 to 42) weeks and were scored for abnormality in a blinded manner using an established MRI scoring system.

RESULTS—Twenty-eight (46.7%) infants had a normal MRI or mild brain abnormality, while 32 (53.3%) infants had moderate-to-severe brain abnormality. Univariate regression analysis demonstrated an association between severity of brain abnormality and quantitative measures of left and right SEF₉₀ and bandwidth span ($\beta = -0.38, -0.40$ and 0.30 , respectively) and qualitative measures of cyclicity, continuity and total Burdjalov score ($\beta = -0.10, -0.14$ and -0.12 , respectively). After correcting for confounding variables, the relationship between MRI abnormality score and aEEG measures of SEF₉₀, bandwidth span and Burdjalov score remained significant.

CONCLUSION—Brain abnormalities on MRI at TEA in premature infants are associated with abnormalities on term aEEG measures, suggesting that anatomical brain injury may contribute to delay in functional brain maturation as assessed using aEEG.

Correspondence: Dr NM El Ters, Division of Newborn Medicine, Department of Pediatrics, Washington University School of Medicine, 1 Children's Place, Campus Box 8116, St Louis, MO 63110, USA. elters_n@kids.wustl.edu.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

INTRODUCTION

The incidence of prematurity in the United States remains high, accounting for one in nine live births each year.¹ Preterm infants are at high risk for brain injury, including intraventricular hemorrhage (IVH) and white matter injury, which contribute to poor neurodevelopmental outcomes.² Magnetic resonance imaging (MRI) provides improved sensitivity to cranial ultrasound in delineating the anatomical location and extent of brain injury. In premature infants, anatomical brain injury on MRI at term equivalent age (TEA) has shown reasonable specificity (79 to 89%) for predicting adverse neurodevelopmental outcomes, including cerebral palsy and cognitive impairment.^{3–6} In contrast, brain function is evaluated using electroencephalography (EEG) and amplitude-integrated electroencephalograph (aEEG). Acute and chronic EEG changes within the first month of life in preterm infants have been shown to correlate with neurodevelopmental delay and cerebral palsy.^{7–10}

Limited-channel aEEG yields recordings that can be interpreted by clinical caregivers at the bedside and has been used in preterm infants to evaluate brain maturation and to predict short- and long-term outcomes.^{11,12} High-grade IVH and periventricular leukomalacia impact aEEG measures of cyclicality, continuity and spectral edge frequency (SEF₉₀) in the first few days of life.^{13–15} The Burdjalov score has been developed to assess developmental maturation on aEEG.¹⁶ Although EEG tools have been used extensively to study term and preterm infants in a variety of clinical contexts, the relationship between aEEG measures and brain injury, detected by MRI, at TEA in extreme premature infants remains unknown.

The objective of this study was to evaluate the impact of brain injury, defined using a standard MRI abnormality scoring tool, on quantitative and qualitative aEEG measures performed at TEA. We hypothesized that these measures of cyclicality, continuity and SEF₉₀ will be lower in babies with moderate-to-severe brain abnormalities than in babies with normal or mild abnormalities on MRI.

METHODS

Study population

Following written, informed parental consent, we recruited a cohort of premature infants born at < 30 weeks of gestation and with moderate-to-severe MRI abnormalities on a TEA MRI scan. A contemporaneous group of gestational age (GA)-matched control infants also born at < 30 weeks of gestation with none/mild abnormalities on MRI was also recruited. Both cohorts of infants were part of an ongoing longitudinal brain monitoring and neuroimaging study and had TEA aEEG recording and MRI scans performed on the same day (Figure 1). All infants were admitted to the neonatal intensive care unit of St Louis Children's Hospital between 2007 and 2015. Infants were excluded from the study if found to have a chromosomal abnormality, congenital central nervous system malformations or suspected/proven congenital infection (for example, HIV, toxoplasmosis, rubella, herpes simplex or cytomegalovirus). The study was conducted with approval from Washington University School of Medicine Human Research Protection Office.

Perinatal and neonatal factors were collected from the medical chart (Table 1).

aEEG recording

Two sets of hydrogel electrodes (Natus Newborn Care, San Carlos, CA, USA) were applied in the C3–P3 and C4–P4 positions for the newborn infant according to the International 10–20 System. Tracings were recorded using the BrainZ BRM3 monitor (Natus Newborn Care) and analyzed offline using the software AnalyZe (Natus Newborn Care).

aEEG recordings were visually inspected to identify a region with low impedance ($< 15 \text{ K}\Omega$) that was free of movement or muscle artifacts to be used for analysis. The most stable, artifact-free and uninterrupted 60 min from the overall recording were used for quantitative analysis.

Quantitative analysis of aEEG—The minimum mean amplitudes, maximum mean amplitudes and bandwidth span (the difference between the maximum mean and the minimum mean amplitudes) of the aEEG tracing were calculated using AnalyZe. SEF₉₀ of the right and left hemispheres, defined as the frequency below which 90% of the spectral power was present, was calculated using the same 60-min recording.

Qualitative analysis of aEEG—Visual inspection of the whole aEEG recording was carried out by a trained observer (NMET) blinded to the clinical information of the patient and to their neuroimaging results. The Burdjalov score¹⁶ was computed after inspecting the following four components (continuity, cyclicity, amplitude of the lower border and bandwidth span). Qualitative scoring was computed by two independent, trained and blinded observers (NMET and SML) and an interclass correlation coefficient was computed.

Neuroimaging

On the same day of the aEEG recording, infants underwent a non-sedated, non-contrast brain MRI following our institutional neonatal MRI guidelines.¹⁷ T1 and T2 images were obtained using Siemens TIM Trio 3.0 T MRI scanner (Siemens Medical Solutions, Erlangen, Germany).

An MRI scoring tool adapted from Kidokoro *et al.*¹⁸ was used, which combines quantitative and qualitative measurements of brain abnormalities in preterm infants at TEA. The quantitative scoring included: dilated lateral ventricles dimensions (score 0 to 3), biparietal diameter (corrected to the GA, scored 0 to 3), interhemispheric distance (score 0 to 3), deep gray matter volume (corrected to the GA, scored 0 to 3), and cerebellar volume (corrected to the GA and scored 0 to 3). Qualitative scoring included: white matter cystic lesions, white matter focal signal abnormality, myelination delay, cortical gray matter signal abnormality, gyral maturation, deep gray matter signal abnormality, and cerebellar signal abnormality. The variables were scored by an experienced reader (AMM) blinded to the clinical information of the patients and the corresponding aEEG measures. The abnormality scoring system was divided into four grades: normal (0 to 3), mild (4 to 7), moderate (8 to 11), and severe (> 12), for the preterm brain at TEA.

Statistical analysis

Perinatal characteristics and electrophysiological measures were compared between the two groups of infants using independent samples *t*-test for continuous variables and χ^2 square or Fischer exact tests for categorical variables. The association between individual quantitative and qualitative aEEG measures and radiographic brain injury was evaluated by using linear regression for the quantitative measures and binary logistic regression for the qualitative measures due to the unequal between-group variance. The standardized coefficient β values along with their significance value and R^2 values are reported for linear regression models, while the coefficient β values, odds ratios (ORs), associated confidence intervals (CIs) and their significance value are reported for logistic regression models.

We also screened for additional known confounding clinical factors that could independently affect aEEG measures at TEA. These included the presence of a ventriculo-peritoneal shunt, antiepileptic medications and breastfeeding status at the time of the aEEG. These variables likely affect the EEG by independent mechanisms that may not be reflected in MRI injury.^{19–23} These factors were included in the multivariate regression model. A *P*-value < 0.05 was considered statistically significant. All statistical calculations were carried out using IBM SPSS Statistics, Version 22 (IBM, Armonk, NY, USA).

RESULTS

Sixty infants were recruited for the study with a mean GA of 26±2 weeks and mean birthweight of 867 ± 268 g. The length of the recordings had a median of 3 (range: 1.5 to 4) h. MRI scans and aEEG recordings were obtained at a mean corrected age of 38.0 weeks GA (range: 37 to 42 weeks GA). A total of 46.7% (28/60) of the infants had either no or mild brain injury, while 53.3% (32/60) had moderate-to-severe injury on MRI. None of our subjects received sedation or caffeine at the time of the aEEG but one subject was receiving phenobarbital. See Table 1 for a comparison of infants with no or mild and moderate-to-severe brain injury. Inter-rater reliability for qualitative scoring of aEEG was excellent with interclass correlation coefficient of 0.937 and *P* < 0.001.

Association of aEEG measures with MRI brain abnormality

(SEF90 was lower in patients with moderate-to-severe brain abnormality on MRI than those with none or mild abnormality (*P* = 0.01 and 0.008 for the left and right SEF₉₀, respectively). There was also a difference in the bandwidth span between infants with no injury/mild injury and infants with moderate/severe injury. Cyclicity, continuity and total Burdjalov scores were lower in the patients with moderate-to-severe MRI abnormality (*P* = 0.005, 0.02 and 0.001, respectively). All results are shown in Table 2.

In the regression analysis, left and right SEF90 showed an association with brain abnormality score with lower values of SEF₉₀ correlating with higher abnormality scores (*F* = 9.89, β = - 0.38, *P* = 0.003 for left SEF₉₀ and *F* = 11.26, β = - 0.40, *P* = 0.001 for right SEF₉₀). Bandwidth span also showed a strong relationship with brain abnormality score (*F* = 6.10, β = 0.30, *P* = 0.01). Using logistic regression, cyclicity, continuity and total Burdjalov scores also showed a strong negative relationship with brain abnormality scores on MRI (β =

-0.10 , OR = 0.90, $P=0.01$ for cyclicity, $\beta = -0.14$, OR = 0.86, $P=0.02$ for continuity and $\beta = -0.12$, OR = 0.88, $P=0.004$ for total Burdjalov score) (Table 3).

Multivariate model

In multivariate regression analysis, MRI abnormality score maintained a significant association with SEF₉₀, bandwidth span and total Burdjalov score after adjusting for postmenstrual age (PMA), presence of ventriculo-peritoneal shunt, administration of antiepileptics drugs and breastfeeding status. We found that MRI score coefficients were significant in this model: $\beta = -0.35$ and $P=0.03$ ($B = -0.06$, 95% CI $(-0.1, -0.01)$) for left SEF₉₀, $\beta = -0.35$ and $P=0.03$ ($B = -0.05$, 95% CI $(-0.1, -0.01)$) for right SEF₉₀, $\beta = 0.45$ and $P=0.006$ ($B = 0.2$, 95% CI $(0.05 \text{ to } 0.3)$) for bandwidth span, and $\beta = -0.14$ and $P=0.02$ (OR = 0.8, 95% CI $(0.7 \text{ to } 0.9)$) for total Burdjalov score.

DISCUSSION

To our knowledge, this study is the first to evaluate the association between qualitative and quantitative aEEG characteristics at TEA and brain injury in preterm newborns and demonstrates a functional maturational delay in EEG activity in babies with moderate-to-severe brain injury. Our results showed that brain injury in premature babies affects the SEF₉₀, bandwidth span cyclicity and total Burdjalov score. SEF₉₀ values were lower in babies with moderate-to-severe injury and this relationship remains significant after correcting for confounding variables. Total Burdjalov score is also associated with MRI severity grade with lower values seen in patients with moderate-to-severe abnormality scores. MRI detected brain abnormalities at TEA in premature infants offer a cross-sectional reflection of events in the perinatal period and neonatal intensive care unit stay. A number of clinical factors have been implicated in the causation of these injuries and include severe-grade IVH, sepsis, severe bronchopulmonary dysplasia, postnatal steroid exposure and necrotizing enterocolitis.^{24,25} Although there is extensive data about early aEEG abnormalities in the acute setting in the neonatal intensive care unit, our results indicate that MRI injury and other clinical factors may also mediate a maturational delay in aEEG measures in this population at TEA.

In our study, cyclicity scores were lower in newborns with moderate-to-severe injury. Burdjalov *et al.*¹⁶ found that the presence of sleep-wake (SW) cycling had the strongest correlation with postconceptional age, and its presence indicates cerebral maturation and a higher level of integrity between the different central nervous system functions. Multiple studies have shown that the presence of SW cycling in preterm babies matures with age.^{26,27} In term newborns with hypoxic-ischemic encephalopathy, early emergence of SW cycles is associated with improved neurodevelopmental outcomes.²⁸ In preterm babies, absent or decreased cyclicity early after birth is associated with brain lesions and long-term adverse neurodevelopmental outcomes.^{12,14,29} Natalucci *et al.*³⁰ showed that there is a delay in the maturation of the SW cycling in the first 4 days of life in preterm infants with severe cerebral lesions compared with infants with mild lesions. Our results indicate that abnormal cyclicity persists until TEA in preterm babies with moderate-to-severe brain abnormality. We hypothesize that the brain integrative function is immature due to brain injury in these

babies. Sohn *et al.*³¹ conducted serial Burdjalov scoring in premature infants with intraventricular hemorrhage early in the clinical course through 36 weeks PMA. They found that the total Burdjalov scores and cyclicity scores at 36 weeks PMA were significantly lower in subjects who sustained IVH grade IV, with abnormal EEG measures correlating most strongly with the presence of seizures, administration of antiepileptic drugs and insertion of external ventricular drains.³¹ In contrast, our study included cross-sectional evaluation of aEEG and MRI-detected brain injury at TEA. The use of MRI as opposed to cranial ultrasound scans enhances the detection of sequelae of severe-grade IVH and in addition provides details of brain injury and subsequent abnormal brain development.³² Our data show that cyclicity and Burdjalov scores were lower in infants with moderate-to-severe brain injury, regardless of the severity of IVH, and this finding could reflect more widespread injury affecting brain maturation in this population. The differences in the aEEG results between the two cohorts, while statistically significant, do appear small. However, in the Burdjalov maturational scoring system, small differences in the total score correspond to significant differences in maturation. For example, a total score of 11 corresponds to a GA of 34 weeks, and a maximum score of 13 corresponds to 39 weeks GA. Emergence of organized SW cycling likely requires complex interactions among neuronal networks that may be vulnerable to perinatal brain injury.³³ Our findings are compatible with the idea that brain lesions can affect the development of these complex connections and can lead to delay in maturation of state cycling.

SEF₉₀ is considered a marker of cerebral maturation and increases with GA in healthy newborns as well as in fetal lambs.^{34,35} Inder *et al.*¹⁵ showed significant lower values in SEF₉₀ in preterm babies in the first 20 days of life with moderate and cystic white matter injury (SEF = 6.0 to 7.9 Hz) compared with newborns with mild white matter injury or normal MRI (SEF = 9.9 to 11.2 Hz). Our cohort shows that SEF₉₀ at TEA continues to be lower in infants with moderate-to-severe brain injury. Our data suggest that, although the SEF₉₀ increased with increasing PMA in both groups, the increase was significantly lower in the group with brain injury. The difference between the two cohorts was significant but small in magnitude. Whether this is clinically significant is not known yet, but it may indicate a trend toward a delay in maturation, especially that the above-mentioned studies showed that SEF₉₀ values tend to increase with cerebral maturation. Other authors^{36,37} have noted that the SEF₉₀ increased from 5.4 to 12 Hz over a period of 10 weeks (from 30 to 40 weeks PMA) of maturation equating to about 0.6 Hz per week of maturation. We found in our cohort that infants with moderate-to-severe brain injury had lower values (SEF₉₀ = 8.8 vs 9.5 Hz), indicating a delay of about 1 to 2 weeks in maturation. SEF₉₀ is a quantitative and reproducible measure that can be used for assessment of functional maturation at TEA in preterm infants with moderate-to-severe brain injury.

Several investigators^{16,38–40} have shown that the bandwidth span gets narrower with age in preterm infants at serial PMA, indicating a greater degree of maturation. Our study showed that bandwidth span and continuity are significantly affected by brain injury but to a lesser extent than SEF. Newborns with normal MRI or mild brain injury have a smaller bandwidth span, indicating a greater maturity and continuity in this cohort of patients.¹⁶ Bandwidth span, another marker of maturation, has a lower discriminatory power in determining maturation with a bandwidth span of < 15 μ V being considered appropriate in term infants.

This study has some limitations. It consisted of a relatively small sample size and the findings will need to be validated in a larger prospective cohort of infants. The R^2 values obtained in the statistical model are modest and this association between aEEG measures and MRI injury needs validation in a larger cohort. The aEEG recording duration varied considerably between subjects although we only included recordings with a minimum length of recording that allows scoring. In addition, MRI scans were scored by one experienced reader. Although the reviewer was blinded to the aEEG findings, this can contribute to the analytical bias.

We found significant maturational delays on aEEG measures in premature infants with moderate-to-severe MRI brain injury at TEA. We hypothesize that a delay in aEEG maturation represents a delay in functional development associated with brain injury. These findings reflect the potential of aEEG as an additional tool in the identification of preterm infants at risk of adverse neurodevelopmental outcomes at TEA.

Acknowledgments

We thank Mike Wallendorf, Jim Alexopoulos and Anthony Barton for their help in data collection, organization and processing. This work was funded by (1) Intellectual and Developmental Disabilities Research Center (IDDRC) at Washington University (NIH/NICHD P30 HD062171), (2) Washington University Institute of Clinical and Translational Sciences KL2 Training Program (NIH/NCATS KL2 TR000450), (3) The Barnes-Jewish Hospital Foundation and the Washington University Institute of Clinical and Translational Sciences Clinical and Translational Funding Program (NIH/NCATS UL1 TR000448), (4) R01 HD057098 and (5) The Dana Foundation, Cerebral Palsy International Research Foundation, Child Neurology Foundation.

References

1. McCabe ER, Carrino GE, Russell RB, Howse JL. Fighting for the next generation: US prematurity in 2030. *Pediatrics*. 2014; 134(6):1193–1199. [PubMed: 25367536]
2. Mukerji A, Shah V, Shah PS. Periventricular/intraventricular hemorrhage and neurodevelopmental outcomes: a meta-analysis. *Pediatrics*. 2015; 136(6):1132–1143. [PubMed: 26598455]
3. Smyser CD, Kidokoro H, Inder TE. Magnetic resonance imaging of the brain at term equivalent age in extremely premature neonates: to scan or not to scan? *J Paediatr Child Health*. 2012; 48(9):794–800. [PubMed: 22970674]
4. Valkama AM, Paakko EL, Vainionpaa LK, Lanning FP, Ilkko EA, Koivisto ME. qMagnetic resonance imaging at term and neuromotor outcome in preterm infants. *Acta Paediatr*. 2000; 89(3):348–355. [PubMed: 10772285]
5. Mirmiran M, Barnes PD, Keller K, Constantinou JC, Fleisher BE, Hintz SR, et al. Neonatal brain magnetic resonance imaging before discharge is better than serial cranial ultrasound in predicting cerebral palsy in very low birth weight preterm infants. *Pediatrics*. 2004; 114(4):992–998. [PubMed: 15466096]
6. Woodward LJ, Anderson PJ, Austin NC, Howard K, Inder TE. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. *N Engl J Med*. 2006; 355(7):685–694. [PubMed: 16914704]
7. Maruyama K, Okumura A, Hayakawa F, Kato T, Kuno K, Watanabe K. Prognostic value of EEG depression in preterm infants for later development of cerebral palsy. *Neuropediatrics*. 2002; 33(3):133–137. [PubMed: 12200742]
8. Marret S, Parain D, Jeannot E, Eurin D, Fessard C. Positive rolandic sharp waves in the EEG of the premature newborn: a five year prospective study. *Arch Dis Child*. 1992; 67(7):948–951. [PubMed: 1519962]
9. Okumura A, Hayakawa F, Kato T, Kuno K, Watanabe K. Developmental outcome and types of chronic-stage EEG abnormalities in preterm infants. *Dev Med Child Neurol*. 2002; 44(11):729–734. [PubMed: 12418612]

10. Hellstrom-Westas L, Rosen I. Electroencephalography and brain damage in preterm infants. *Early Hum Dev.* 2005; 81(3):255–261. [PubMed: 15814207]
11. Klebermass K, Olischar M, Waldhoer T, Fuiko R, Pollak A, Weninger M. Amplitude-integrated EEG pattern predicts further outcome in preterm infants. *Pediatr Res.* 2011; 70(1):102–108. [PubMed: 21436758]
12. Hellstrom-Westas L, Klette H, Thorngren-Jerneck K, Rosen I. Early prediction of outcome with aEEG in preterm infants with large intraventricular hemorrhages. *Neuropediatrics.* 2001; 32(6): 319–324. [PubMed: 11870588]
13. Bowen JR, Paradisis M, Shah D. Decreased aEEG continuity and baseline variability in the first 48 hours of life associated with poor short-term outcome in neonates born before 29 weeks gestation. *Pediatr Res.* 2010; 67(5):538–544. [PubMed: 20098343]
14. Kidokoro H, Kubota T, Hayashi N, Hayakawa M, Takemoto K, Kato Y, et al. Absent cyclicality on aEEG within the first 24 h is associated with brain damage in preterm infants. *Neuropediatrics.* 2010; 41(6):241–245. [PubMed: 21445813]
15. Inder TE, Buckland L, Williams CE, Spencer C, Gunning MI, Darlow BA, et al. Lowered electroencephalographic spectral edge frequency predicts the presence of cerebral white matter injury in premature infants. *Pediatrics.* 2003; 111(1):27–33. [PubMed: 12509550]
16. Burdjalov VF, Baumgart S, Spitzer AR. Cerebral function monitoring: a new scoring system for the evaluation of brain maturation in neonates. *Pediatrics.* 2003; 112(4):855–861. [PubMed: 14523177]
17. Mathur AM, Neil JJ, McKinstry RC, Inder TE. Transport, monitoring, and successful brain MR imaging in unsedated neonates. *Pediatr Radiol.* 2008; 38(3):260–264. [PubMed: 18175110]
18. Kidokoro H, Neil JJ, Inder TE. New MR imaging assessment tool to define brain abnormalities in very preterm infants at term. *AJNR Am J Neuroradiol.* 2013; 34(11):2208–2214. [PubMed: 23620070]
19. Bell AH, Greisen G, Pryds O. Comparison of the effects of phenobarbitone and morphine administration on EEG activity in preterm babies. *Acta Paediatr.* 1993; 82(1):35–39. [PubMed: 8453218]
20. Deoni SC, Dean DC 3rd, Piryatinsky I, O’Muircheartaigh J, Waskiewicz N, Lehman K, et al. Breastfeeding and early white matter development: a cross-sectional study. *Neuroimage.* 2013; 82:77–86. [PubMed: 23721722]
21. Lee HJ, Kim HS, Kim SY, Sim GH, Kim ES, Choi CW, et al. Effects of postnatal age and aminophylline on the maturation of amplitude-integrated electroencephalography activity in preterm infants. *Neonatology.* 2010; 98(3):245–253. [PubMed: 20414001]
22. van Leuven K, Groenendaal F, Toet MC, Schobben AF, Bos SA, de Vries LS, et al. Midazolam and amplitude-integrated EEG in asphyxiated full-term neonates. *Acta Paediatr.* 2004; 93(9):1221–1227. [PubMed: 15384888]
23. Young GB, da Silva OP. Effects of morphine on the electroencephalograms of neonates: a prospective, observational study. *Clin Neurophysiol.* 2000; 111(11):1955–1960. [PubMed: 11068229]
24. Shah DK, Doyle LW, Anderson PJ, Bear M, Daley AJ, Hunt RW, et al. Adverse neurodevelopment in preterm infants with postnatal sepsis or necrotizing enterocolitis is mediated by white matter abnormalities on magnetic resonance imaging at term. *J Pediatr.* 2008; 153(2):170–175 e1. [PubMed: 18534228]
25. Neubauer V, Junker D, Griesmaier E, Schocke M, Kiechl-Kohlendorfer U. Bronchopulmonary dysplasia is associated with delayed structural brain maturation in preterm infants. *Neonatology.* 2015; 107(3):179–184. [PubMed: 25632975]
26. Sisman J, Campbell DE, Brion LP. Amplitude-integrated EEG in preterm infants: maturation of background pattern and amplitude voltage with postmenstrual age and gestational age. *J Perinatol.* 2005; 25(6):391–396. [PubMed: 15815708]
27. Olischar M, Klebermass K, Kuhle S, Hulek M, Kohlhauser C, Rucklinger E, et al. Reference values for amplitude-integrated electroencephalographic activity in preterm infants younger than 30 weeks’ gestational age. *Pediatrics.* 2004; 113(1 Pt 1):e61–e66. [PubMed: 14702497]

28. Osredkar D, Toet MC, van Rooij LG, van Huffelen AC, Groenendaal F, de Vries LS. Sleep-wake cycling on amplitude-integrated electroencephalography in term newborns with hypoxic-ischemic encephalopathy. *Pediatrics*. 2005; 115(2):327–332. [PubMed: 15687440]
29. Olischar M, Klebermass K, Waldhoer T, Pollak A, Weninger M. Background patterns and sleep-wake cycles on amplitude-integrated electroencephalography in preterms younger than 30 weeks gestational age with peri-/intraventricular haemorrhage. *Acta Paediatr*. 2007; 96(12):1743–1750. [PubMed: 17971193]
30. Natalucci G, Rousson V, Bucher HU, Bernet V, Hagmann C, Latal B. Delayed cyclic activity development on early amplitude-integrated EEG in the preterm infant with brain lesions. *Neonatology*. 2013; 103(2):134–140. [PubMed: 23207184]
31. Sohn JA, Kim HS, Lee EH, Lee J, Lee JA, Choi CW, et al. Developmental change of amplitude-integrated electroencephalographic activity in preterm infants with intraventricular hemorrhage. *Early Hum Dev*. 2013; 89(12):961–966. [PubMed: 24083894]
32. de Vries LS, Benders MJ, Groenendaal F. Imaging the premature brain: ultrasound or MRI? *Neuroradiology*. 2013; 55(Suppl 2):13–22. [PubMed: 23839652]
33. Scher MS. Ontogeny of EEG sleep from neonatal through infancy periods. *Handb Clin Neurol*. 2011; 98:111–129. [PubMed: 21056183]
34. Bell AH, McClure BG, McCullagh PJ, McClelland RJ. Spectral edge frequency of the EEG in healthy neonates and variation with behavioural state. *Biol Neonate*. 1991; 60(2):69–74. [PubMed: 1932388]
35. Szeto HH. Spectral edge frequency as a simple quantitative measure of the maturation of electrocortical activity. *Pediatr Res*. 1990; 27(3):289–292. [PubMed: 2320398]
36. Song J, Zhu C, Xu F, Guo J, Zhang Y. Predictive value of early amplitude-integrated electroencephalography for later diagnosed cerebral white matter damage in preterm infants. *Neuropediatrics*. 2014; 45(5):314–320. [PubMed: 25003781]
37. Niemarkt HJ, Jennekens W, Pasman JW, Katgert T, Van Pul C, Gavilanes AW, et al. Maturation changes in automated EEG spectral power analysis in preterm infants. *Pediatr Res*. 2011; 70(5):529–534. [PubMed: 21772227]
38. Zhang D, Liu Y, Hou X, Zhou C, Luo Y, Ye D, et al. Reference values for amplitude-integrated EEGs in infants from preterm to 3.5 months of age. *Pediatrics*. 2011; 127(5):e1280–e1287. [PubMed: 21482614]
39. Hellstrom-Westas L, Rosen I, de Vries LS, Greisen G. Amplitude-integrated EEG classification and interpretation in preterm and term infants. *NeoReviews*. 2006; 7(2):e76–e87.
40. Thornberg E, Thiringer K. Normal pattern of the cerebral function monitor trace in term and preterm neonates. *Acta Paediatr Scand*. 1990; 79(1):20–25. [PubMed: 2316356]

Figure 1.

Amplitude-integrated electroencephalograph (aEEG) recordings with the corresponding magnetic resonance imaging (MRI) images of two patients. The top panel depicts a continuous aEEG, with the presence of cyclicity, and the corresponding MRI image with no noted abnormalities. The bottom panel depicts a continuous aEEG with no definite cyclicity and an abnormal MRI with white matter cystic lesions and an abnormality score of 25.

Table 1

Neonatal characteristics of the cohort

	Severe/moderate MRI score (<i>n</i> = 32)	Mild/normal MRI score (<i>n</i> =28)	<i>P</i> -value
Birth weight (mean ± s.d.)	857±284	879 ± 253	0.75
Gestational age (mean ± s.d.)	25.6 ± 2.1	26.2 ± 1.9	0.30
Postmenstrual age (mean ± s.d.)	39.2 ± 1	38.2 ± 1	0.03 ^a
CRIB-II score (mean ± s.d.)	11.06 ± 3.6	10.4 ± 3.7	0.48
NEC surgery, <i>n</i> (%)	7 (11.7%)	3 (5.0%)	0.31
PDA ligation, <i>n</i> (%)	7 (11.7%)	1 (1.7%)	0.06
ROP surgery, <i>n</i> (%)	13 (21.7%)	3 (5.0%)	0.009 ^a
Postnatal steroids, <i>n</i> (%)	10 (16.7%)	7 (11.7%)	0.59
Antiepileptic drugs at term, <i>n</i> (%)	1 (1.7%)	0 (0.0%)	1.00
VP shunt or reservoir at term, <i>n</i> (%)	12 (20.0%)	1 (1.7%)	0.001 ^a
Sepsis, <i>n</i> (%)	22 (36.7%)	8 (13.3%)	0.002 ^a
Oxygen therapy at 36 weeks, <i>n</i> (%)	28 (46.7%)	20 (33.3%)	0.12
Inotropes, <i>n</i> (%)	18 (30.0%)	11(18.3%)	0.19
IVH grade 3–4, <i>n</i> (%)	23 (38.3%)	3 (5.0 %)	0.001 ^a
Breastfeeding status	9 (15%)	11 (18.3%)	0.3

Abbreviations: CRIB-II, Clinical Risk Index for Babies; IVH, intraventricular hemorrhage; MRI, magnetic resonance imaging; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; VP shunt, ventriculo-peritoneal shunt.

^aDenotes significance at $P < 0.05$.

Table 2

Quantitative and qualitative aEEG measures among the two groups

	Severe/moderate MRI score	Mild/normal MRI score	P-value
Left hemisphere SEF ₉₀	8.8 (±1.2)	9.5 (±1.0)	0.01 ^a
Right hemisphere SEF ₉₀	8.7 (±1.1)	9.5 (±0.8)	0.008 ^a
Bandwidth span	9.6 (±3.0)	8.1 (±2.3)	0.03 ^a
Continuity score	1.8 (±0.3)	2.0 (±0.0)	0.02 ^a
Cyclicity score	3.2 (±0.9)	3.9 (±0.8)	0.005 ^a
Amplitude of LB	1.9 (±0.1)	2.0 (±0.0)	0.35
BS and amplitude of LB	3.9 (±0.2)	4.0 (±0.0)	0.16
Total Burdjalov score	11.0 (±1.2)	11.9 (±0.8)	0.001 ^a

Abbreviations: aEEG, amplitude-integrated electroencephalograph; BS, bandwidth span; LB, lower border; MRI, magnetic resonance imaging; SEF₉₀, spectral edge frequency. Values represent means ± s.d.

^aDenotes significance at $P < 0.05$.

Table 3

Coefficient values corresponding to the regression models of each of the quantitative and qualitative measures of aEEG with MRI scores

aEEG measure	β -value	B-value (95% CI for B)	P-value
Left SEF ₉₀	-0.38	-0.06 (-0.1, -0.02)	0.003 ^a
Right SEF ₉₀	-0.40	-0.06 (-0.1, -0.02)	0.001 ^a
Bandwidth span	0.30	0.1 (0.02, 0.2)	0.01 ^a
aEEG measure	β -Value	OR (95% CI for OR)	P-value
Cyclicity	-0.10	0.90 (0.83, 0.97)	0.01 ^a
Continuity	-0.14	0.86 (0.76, 0.98)	0.02 ^a
Burdjalov score	-0.12	0.88 (0.81, 0.95)	0.004 ^a

Abbreviations: aEEG, amplitude-integrated electroencephalograph; CI, confidence interval; MRI, magnetic resonance imaging; OR, odds ratio; SEF₉₀, spectral edge frequency. Values represent means $\pm$ s.d.

^aDenotes significance at $P < 0.05$.