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Normative Amplitude Integrated EEG (aEEG) Measures in Preterm Infants

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Abstract

Objective—Assessing qualitative patterns of amplitude integrated EEG (aEEG) maturation of preterm infants requires personnel with training in interpretation and an investment of time. Quantitative algorithms provide a method for rapidly and reproducibly assessing an aEEG recording independent of provider skill level. Although there are several qualitative and quantitative normative datasets in the literature, this study provides the broadest array of quantitative aEEG measures in a carefully selected and followed cohort of preterm infants with mild or no visible injury on term equivalent MRI and subsequently normal neurodevelopment at 2 and 7 years of age.

Study Design—A two-channel aEEG recording was obtained on days 4,7,14, and 28 of life for infants born 30 weeks EGA. Measures of amplitude and continuity, spectral edge frequency, percentage of trace in interburst interval, interburst interval length, and frequency counts of smooth delta waves, delta brushes and theta bursts were obtained. MRI was obtained at term-equivalent age (TEA) and neurodevelopmental testing was conducted at 2 and 7 years of corrected age.

Result—Correlations were found between increasing post-menstrual age (PMA) and decreasing maximum amplitude ($R=-0.23$, $p=0.05$), increasing minimum amplitude ($R=0.46$, $p=0.002$), and increasing spectral edge frequency ($R=0.78$, $p=4.17 \times 10^{-14}$). Negative correlations were noted between increasing PMA and counts of smooth delta waves ($R=-0.39$, $p=0.001$), delta brushes ($R=-0.37$, $p=0.003$), and theta bursts ($R=-0.61$, $p=5.66 \times 10^{-8}$). Increasing PMA was also

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Conflicts of interest

The authors declare no conflicts of interest.

associated with a decreased amount of time spent in the interburst interval ($R=-0.38$, $p=0.001$) and a shorter length of the maximum IBI ($R=-0.27$, $p=0.03$).

Conclusion—This analysis supports a strong correlation between quantitatively determined aEEG measures and PMA, in a cohort of preterm infants with normal TEA neuroimaging and neurodevelopmental outcomes at 7 years of age, which is both predictable and reproducible. These “normative” quantitative values support the pattern of maturation previously identified by qualitative analysis.

Keywords

spectral edge frequency; Bayesian inference; developmental outcomes; quantitative aEEG

Introduction

Burdjalov et al. developed systematic amplitude integrated EEG (aEEG) interpretation guidelines for the term and preterm neonatal population. This approach uses a subjective review of the aEEG trace to determine the continuity of cerebral activity (i.e. the proportion of activity above a set amplitude threshold), the presence or absence of sleep-wake cycling, the minimum amplitude or “baseline” of the trace, as well as the difference between the minimum and maximum amplitudes (1). In addition, other work has demonstrated that there is a clear qualitative pattern of maturation in the aEEG traces of premature infants without neurodevelopmental impairment which parallels that of their overall development (2,3) and that this analysis can also be used to predict outcomes (4).

Digitally recorded aEEG traces allow for computation of a broad array of signal characteristics that can be readily compared across a cohort. The simplest measures, minimum, maximum, and mean amplitude, allow for assessment of continuity. Fast Fourier transformation, which decomposes a complex signal into individual frequencies, enables a more granular view into the exact distribution of activity within a defined frequency band. Pattern recognition algorithms can identify characteristic electrographic signals that evolve in parallel with overall development, such as the length of time between bursts (the interburst interval or IBI) or specific wave patterns such as delta waves, whose appearance in a neonatal aEEG is developmentally regulated. The value of an automated quantitative approach to aEEG interpretation has been discussed in several different forums (4–6) and has been applied largely to automated seizure detection algorithms with some remarkable success (7–11).

A remaining challenge, which must be overcome for widespread adoption of quantitative aEEG techniques, is the development of a ‘normative’ dataset for comparison. Thornberg and Thiringer published one of the earliest datasets (12); however, they did not record any infants born before 30 weeks EGA, had no long term neurodevelopmental data, and reported only the minimum and maximum voltages. Natalucci et al. published data (13) demonstrating predictable changes in amplitude characteristics over a broader range of gestational ages and included term-equivalent imaging as the measure of outcome. Nevertheless, these data are confounded by collection only during the first 96 hours of life, a limited number of quantitative measures, and no long-term neurodevelopmental data.

Niemarkt et al. described an even broader array of amplitude (5) and spectral characteristics (14) which was collected longitudinally in a cohort of 18 preterm infants who subsequently had developmental testing scores within the normal range at 1 and 2 years of corrected age (CA), respectively. However there is emerging concern (15) that neurodevelopmental testing at 2 years of age does not accurately predict outcomes at school-age or beyond, and no further follow-up data is available.

To address these issues, we designed a study that outlines a full array of quantitative aEEG characteristics, including amplitude, spectral, and wave pattern features, in a carefully selected population of preterm infants with favorable neuroimaging at term equivalent age and neurodevelopmental outcomes at 2 and 7 years of age. We aim to establish a “normative” range of aEEG measures for this population and hypothesize that healthy preterm infants will demonstrate a predictable pattern of maturation evident by quantitative analysis.

Materials and Methods

Subjects

The subjects in this analysis are a carefully chosen subset of a larger cohort recruited in a prospective monitoring and imaging study conducted by the Victorian Infant Brain Study (ViBeS) group at the Murdoch Children’s Research Institute in Victoria, Australia. Subjects were premature infants born at ≥ 30 completed weeks of gestation and admitted to the Royal Women’s Hospital in Melbourne, Australia between July 2001 and December 2003. Parents of eligible infants were approached either before delivery or as soon as possible after delivery for informed consent.

Inclusion criteria

Other aspects of this cohort have been described elsewhere in the literature (16–18). For the purposes of this study, subjects were included in the analysis if they were determined to meet strictly defined outcome parameters in terms of both radiographic injury and subsequent neurodevelopmental testing. Favorable injury outcome was defined as no greater than grade I IVH on cranial ultrasound and no greater than mild white matter injury on term equivalent MRI (15). Favorable developmental outcome was assessed at two age points, 2 years (Bayley Scales of Infant Development, 2nd Edition [The Psychological Corporation, San Antonio, TX, USA] with both mental developmental index and psychomotor developmental index sub-scores ≥ 85) and at 7 years (Wechsler Abbreviated Scale of Intelligence [The Psychological Corporation, San Antonio, TX, USA] with a score ≥ 85).

Study design

Information regarding the sex, gestational age, birth weight, and Apgar scores were obtained from the subject’s medical chart. Hydrospot electrodes [Physiometrix Inc, North Billerica, MA, USA] were applied in the conventional C3-P3, C4-P4 configuration and traces were recorded using the BRM2 monitor [Natus Medical Incorporated, San Carlos, CA, USA]. Each recording was a minimum of 120 minutes in length and was conducted on days 4, 7, 14 and 28 of life, regardless of gestational age at birth. All quantitative analysis was performed

using Analyze [Natus Medical Incorporated, San Carlos, CA], an offline aEEG review software package.

Cranial ultrasounds were obtained four times during the hospital course: during the first 72 hours, day 7–10, day 28, and prior to discharge as per routine clinical practice. All infants underwent an MRI scan at term equivalent age without sedation. Infants were fed, swaddled, outfitted with earmuffs, and placed in a vacuum fixation beanbag. Sleeping infants were scanned in a 1.5T Signa LX Echospeed MRI System [General Electric, Milwaukee, WI, USA].

Basic Analysis

The recorded aEEG data were visually inspected, and regions of the recording with electrode impedance exceeding 15k Ω were discarded. The middle 60-minutes of each 120-minute recording was used for analysis, with the aim of avoiding artifacts sometimes found at the beginning and end of aEEG recordings. This one-hour segment was then visually reviewed to ensure that it was artifact and seizure-free. The minimum, maximum, and mean amplitude of each trace was then calculated. A sample tracing with quantitative measures highlighted is shown in the top panel of Figure 1.

Continuity

Hellström-Westas and de Vries standardized (2) the terminology used to describe aEEG backgrounds with a five-category system consisting of continuous normal voltage, discontinuous normal voltage, continuous low voltage, burst suppression, and flat tracing. Each category is defined by minimum and maximum voltage parameters. Continuity can be evaluated quantitatively by determining the average baseline of a trace as compared to a predetermined threshold (19) or by determining the percentage of the trace contained within certain voltage thresholds (20). In this dataset, the percentage of two-second intervals where the amplitude of the recorded signal was above four different thresholds (10 μ V, 25 μ V, 50 μ V, 100 μ V) was calculated, thus allowing for background categorization. For example, using the criteria outlined by Hellström-Westas and de Vries, a continuous normal voltage pattern should have nearly 100% of samples with amplitudes above 10 μ V and below 50 μ V. A visual representation of this analysis is depicted in the bottom panel of Figure 1.

Sleep-wake cycling

The trace was inspected for evidence of sleep-wake cycling (SWC), defined as rhythmic sinusoidal elevations of the baseline lasting longer than 20 minutes (21). The SWC pattern was deemed “mature” if it was the predominant pattern during the recording period, “intermediate” if cycling was present but not predominant, and “absent” if SWC was not present.

Spectral edge frequency (SEF) analysis

SEF has been used by researchers to determine the frequency distribution in aEEG traces in healthy (14,20) and injured (22) preterm infants. Fast Fourier transformation was used to determine SEF 90, defined as the frequency between 2 and 20 Hz, below which 90% of the power was present in the same 60-minute epoch.

Bayesian probability analysis

A software algorithm developed by Mitchell et al. (23), using a broader array of the same infants in this cohort, takes a Bayesian inference approach to identify delta waves (including separate components of smooth delta waves and delta brushes) and theta bursts. In addition, it can calculate the percentage of the trace that is spent in the interburst interval (IBI) and the length of the maximum IBI.

Smooth delta waves were defined as a wave pattern at least 100 μ V in amplitude with a frequency between 0.5 Hz and 1.5 Hz. Delta brushes are superimposed waves of higher frequency (8–22 Hz) and lower amplitude (10–75 μ V). Theta bursts were defined as activity greater than 100 μ V in amplitude and between 4 and 6 Hz in frequency. Interburst interval was defined as a period of time greater than five seconds with minimal activity (<10 μ V). Absolute counts of each wave type (delta brush, smooth delta wave and theta burst) as well as the IBI data were measured for the same 60-minute epoch as the previous measurements.

Radiographic analysis

MRI images were analyzed qualitatively for white matter injury by a single investigator (TI) blinded to the infant's clinical history. WMI was graded from 1–4 where grade 1 was normal, grade 2 was mild non-cystic abnormality, grade 3 was moderate-severe non-cystic abnormality and grade 4 was severe cystic abnormality (22).

Statistical analysis

As the sample was drawn from a group of infants with a wide range of gestational ages at birth and was collected across an even wider PMA, the recordings were divided into four groups based on the PMA at the time of aEEG recording (< 27 weeks, 27–29 weeks, 29–31 weeks and > 31 weeks) for some of the analysis. Due to variations in gestational age at birth, some infants had consecutive studies in the same grouping. Within each group, the mean, minimum, and maximum amplitude were calculated as well as the mean SEF 90 and continuity measures. Associations were made between the exact PMA at the time of each recording (rather than group) and each quantitative variable using the Pearson product-moment correlation coefficient. All statistical analysis was conducted using R version 3.1.1 [R Foundation for Statistical Computing, Vienna, Austria] and MATLAB 8.1 [The MathWorks, Inc., Natick, MA, USA].

Results

Descriptive statistics

224/348 (64%) eligible infants born during the recruitment period were successfully enrolled in the initial cohort. 20/224 (9%) met the previously outlined inclusion criteria and had normal neurodevelopmental scores at 2 years of age, but only 18/20 (90%) had normal neurodevelopmental scores at 7 years of age. The characteristics of the included sample are provided in Table 1 and a comparison between those included and excluded is provided in Table 2.

Amplitude measures

Both the minimum and maximum amplitudes were strongly correlated with PMA, with increasing minimum amplitude associated with increasing PMA ($R=0.46$, $p=0.002$) and a decreasing maximum amplitude with increasing PMA ($R=-0.23$, $p=0.05$). Mean amplitude was not significantly associated with PMA. There was also a strong correlation with an increase in the SEF 90 and advancing PMA ($R=0.78$, $p=4.17 \times 10^{-14}$), going from 7.9 to 10.1 Hz over the measured period.

Our data confirm the previously described qualitative measures of aEEG background maturation, demonstrating a decrease in the high frequency activity associated with high voltage bursts ($> 100 \mu\text{V}$) and a simultaneous increase in the percentage of the trace associated with continuous normal voltages (25–50 μV). Table 3 provides a summary of this data.

Sleep-wake cycling

SWC was noted in increasing proportions as PMA advanced, similar in proportion to that noted in prior studies (21). An overview is provided in Table 4.

Delta and Theta activity

A significant negative correlation was noted with increasing PMA and counts of all wave types including smooth delta wave ($R=-0.39$, $p=0.001$), delta brush ($R=-0.37$, $p=0.003$) and theta burst ($R=-0.61$, $p=5.66 \times 10^{-8}$). Median detected wave counts for each gestational age grouping are provided in Table 5.

Interburst interval

The mean percentage of the recording spent in the interburst interval decreased as PMA increased, with a significant negative correlation ($R=-0.38$, $p=0.001$). The maximum length of the interburst interval decreased with increasing PMA, with a significant negative correlation ($R=-0.27$, $p=0.03$). Complete information about changes in the interburst interval at different PMAs is provided in Table 5.

Discussion

A significant limitation preventing the widespread adoption of routine EEG monitoring in neonatal intensive care units is the need for interpretation by skilled epileptologists, adding a significant time and cost burden to health care systems. aEEG has filled this gap in many centers around the world, using pattern recognition to provide information about brain function that can be readily interpreted by non-expert clinicians, enabling detection of electrographic seizures and assessment of background activity (24). Nevertheless, both conventional and aEEG methods rely on subjective interpretation which can be variable, time consuming, and requires a degree of experience.

This study uses quantitative methods on aEEG to confirm the maturational patterns that have been previously described in the literature using qualitative analysis. Our analysis of the content of these aEEG recordings supports a predictable transition that is strongly correlated

with PMA. This developmental continuum transitions from the infrequent high amplitude bursts and long low-voltage quiescent periods of burst suppression and *tracé discontinue*, which predominate the earliest gestational ages, to the continuous, moderate voltage activity with infrequent quiet periods of *tracé alternans* associated with more developmentally mature infants.

These findings have significant biological relevance as there is compelling evidence that early cortical activity is important for brain growth (25), the absence or delay of which can be predicted by a persistent or transient arrest in electrographic maturation (26) and is known to be associated with adverse neurodevelopment (27). More specifically, an increased IBI (and thus overall decreased cortical activity) has been associated with adverse events both in the acute setting such as acidosis (28) or sedative administration such as morphine and phenobarbital (29), as well as long term with an increased likelihood of developmental handicap at 2 years CA (30).

Technical aspects of aEEG signal processing, as is the case with all quantitative aEEG or EEG analysis, limit this study. In order to produce the aEEG output, the raw signal is transformed, first by an asymmetric bandpass filter, which attenuates the signal between 2 and 15 Hz, followed by rectification and averaging over a moving two second time window. This design, while intentionally minimizing the unwanted signals introduced by muscle artifact, also removes the low frequency component of cerebral activity. As a result, the aEEG signal is not a 1:1 representation of a traditionally acquired EEG trace, nor is it intended to be. Nevertheless, the correlation between these quantitatively determined features and PMA is predictable, reproducible, and is remarkably similar to similar examinations made using conventional EEG.

Constructing a longitudinal cohort of former preterm infants with developmental outcomes indistinguishable from the general population is quite challenging. Every step along the way carries the potential risk of exclusion, largely due to death or disability. Indeed, given the NICHD Neonatal Research Network data, only 44% of the infants in this study's cohort, with a mean EGA of 27 weeks, would be expected to survive without major morbidity at the time of hospital discharge (31), much less have a neurodevelopmental outcome within the normal range at school age. As described earlier, Niemarkt et al. constructed a similar longitudinal cohort which examined 4% (18/449) of the initially eligible infants, very similar to the 5% (18/348) discussed in this study, particularly given our collection of an additional time point of data at age 7. These additional data proved quite valuable, as a further testing revealed that 10% of the cohort that appeared to be developing normally at 2 years CA, had fallen behind by school age.

The results of this study have both clinical and research applications. Although this analysis is presented as group data, all 18 infants exhibited the same developmental maturation patterns along a similar trajectory. This reproducibility allows clinicians to use this information as an aid in identifying preterm infants with reassuring aEEG parameters, potentially assisting in the management of the patient or counseling the parents of premature infants. Similarly, these same parameters can be longitudinally tracked in future prospective studies in order to assess the potential impact of a number of frequently encountered clinical

situations that have been associated with adverse neurodevelopmental outcomes such as sepsis, necrotizing enterocolitis, and medications such as morphine, dexmetomidine, and general anesthesia.

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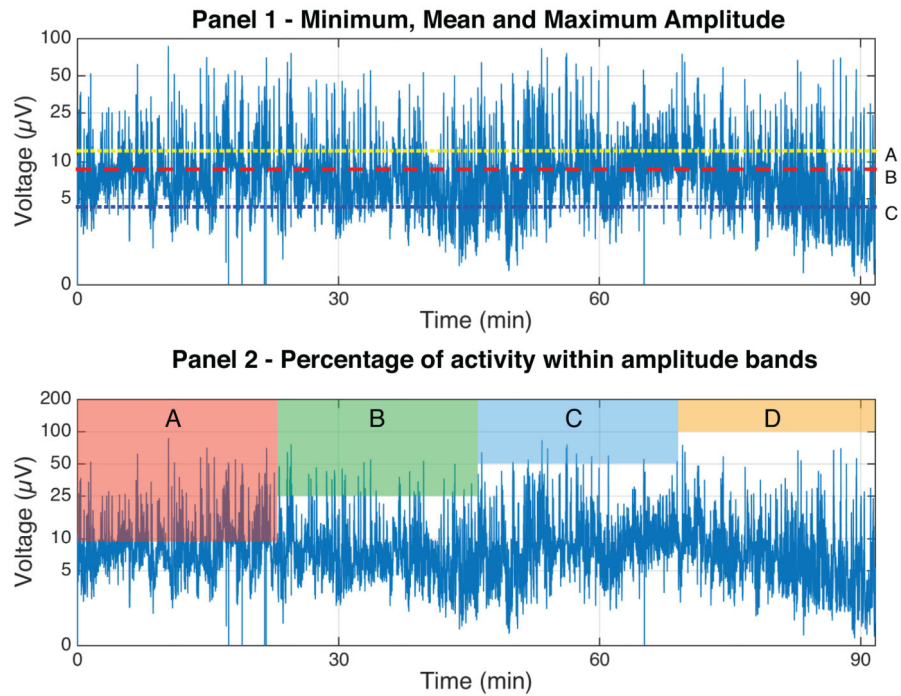


Figure 1.

The top panel depicts a 90-minute aEEG recording. Line A represents the median maximum value (12.3 μV), line B the mean value (8.8 μV) and line C the median minimum value (4.3 μV). The bottom panel depicts the 4 amplitude bands that were assessed in order to determine the content of the trace. Band A represents the percentage of 2 second epochs with a mean value greater than 10 μV , Band B represents those with a mean value greater than 25 μV , Band C represents those with a mean value greater than 50 μV and Band D those greater than 100 μV .

Sample Perinatal and Clinical Characteristics

Characteristic	n=18
Gestational age at birth, $m^1 \pm SD$, weeks	27.3 \pm 1.9
Male, n (%)	9 (50)
Birth weight, $m \pm SD$, g	976 \pm 173
Intraventricular hemorrhage	
None, n (%)	16 (89)
Grade I, n (%)	2 (11)
White matter injury	
None, n (%)	10 (56)
Mild non-cystic, n (%)	8 (44)
Need for inotropic agents, n (%)	4 (22)
Need for sedative agents, n (%)	0 (0)
Antenatal steroids, n (%)	17 (94)
Culture-proven sepsis, n (%)	3 (17)
BPD ² , n (%) ^c	6 (33)
BSID-II	
MDI ³ , $m \pm SD$	98 \pm 9
PDI ⁴ , $m \pm SD$	99 \pm 9
WASIFSIQ, $m \pm SD$	104 \pm 15

¹ m denotes mean, M denotes median.

² Defined as need for supplemental oxygen at 36 weeks PMA.

³ Mental Development Index.

⁴ Psychomotor Development Index.

Table 1

Table 2

Comparison of perinatal factors between included and excluded subjects

	Included (n=18)	Excluded (n=206)	P value
Gestational age at birth, $m \pm SD$, weeks	27.3 \pm 1.9	27.6 \pm 1.9	0.521
Male, n (%)	9 (50)	105 (51)	0.992
Birth weight, $m \pm SD$, g	976 \pm 173	927.6 \pm 197	0.308
Antenatal steroids, n (%)	17 (94)	181 (88)	0.260
Intrauterine growth restriction, n (%)	2 (11)	16 (8)	0.937

¹ Post-menstrual age.

Table 3

Amplitude characteristics by PMA¹

	Group 1 <27 weeks (n=8)	Group 2 27–29 weeks (n=16)	Group 3 29–31 weeks (n=21)	Group 4 >31 weeks (n=19)
Min Amplitude, M^2 (range)	1.7 (1.3–2.8)	2.1 (1.5–2.8)	2.4 (1.1–3.7)	3.1 (2.0–3.5)
Mean Amplitude, M (range)	6.2 (5.6–8.6)	5.8 (4.4–8.3)	6.2 (3.9–8.4)	6.3 (4.7–8.8)
Max Amplitude, M (range)	12.9 (8.6–15.7)	10.7 (5.1–15.9)	10.4 (5.4–15.7)	9.7 (5.5–15.5)
SEF 95 ³ , M (range)	7.9 (7.4–8.8)	8.3 (7.3–9.5)	9.4 (8.6–10.7)	10.1 (9.0–11.2)
> 10 μ V, M (range) ⁴	100 (97–100)	100 (94–100)	100 (88–100)	100 (100–100)
> 25 μ V, M (range) ⁴	76 (64–89)	78 (55–89)	80 (56–93)	87 (71–100)
> 50 μ V, M (range) ⁴	46 (40–59)	44 (30–64)	47 (24–60)	39 (13–69)
> 100 μ V, M (range) ⁴	22 (16–29)	17 (4–28)	12 (1–23)	5 (0–16)

¹ PMA denotes post-menstrual age.

² M denotes median value.

³ Spectral edge frequency.

⁴ Percentage of one-minute epochs with average baseline exceeding given threshold.

Table 4

Sleep-wake cycling by PMA¹

	Group 1 <27 weeks (n=8)	Group 2 27-29 weeks (n=16)	Group 3 29-31 weeks (n=21)	Group 4 >31 weeks (n=19)
SWC ² absent	2	2	0	0
SWC ² intermediate	6	14	16	6
SWC ² mature	0	0	5	13

¹ PMA denotes post-menstrual age.

² SWC denotes sleep-wake cycling.

Table 5

Wave characteristics by PMA¹

	Group 1 <27 weeks (n=8)	Group 2 27–29 weeks (n=16)	Group 3 29–31 weeks (n=21)	Group 4 >31 weeks (n=19)
SDW ² , M ³ (range)	191 (112–315)	167 (57–367)	131 (24–350)	101 (18–254)
DB ⁴ , M (range)	61 (25–74)	47 (5–94)	34 (0–119)	20 (3–70)
TB ⁵ , M (range)	21 (9–36)	7 (0–41)	1 (0–9)	1 (0–6)
IBI ⁶ %, m (SD)	38 (14)	35 (9)	33 (12)	24 (9)
Max. IBI Length, seconds, m (SD)	31 (17)	41 (51)	24 (10)	17 (8)

¹ Post-menstrual age.

² Smooth delta wave.

³ m denotes mean, M denotes median.

⁴ Delta brush.

⁵ Theta burst.

⁶ Percentage of recording time between bursts.