Published in final edited form as:

Early Hum Dev. 2013 December ; 89(12): . doi:10.1016/j.earlhumdev.2013.09.018.

Quantification of Neonatal Amplitude-Integrated EEG Patterns

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Abstract

Background—Amplitude-integrated EEG (aEEG) is increasingly used in research with premature infants; however, comprehensive interpretation is limited by the lack of simple approaches for reliably quantifying and summarizing the data.

Aim—Explore operational measures for quantifying continuity and discontinuity, measured by aEEG as components of infant brain function.

Study design—An exploratory naturalistic study of neonates while in the Neonatal Intensive Care Unit (NICU). One single channel aEEG recording per infant was obtained without disruption of nursing care practices.

Subjects—24 infants with mean postmenstrual age (PMA) 33.11 weeks (SD 3.49), average age 2.62 weeks (SD 1.35) and mean birth weights 1.39kg (SD 0.73).

Outcome Measures—Quantification of continuity and discontinuity included bandwidth and lower border of aEEG, calculated proportion of time with signal amplitude below 10 μ V, and peak counts. Variance of bandwidth and lower border denoted cycling.

Results—Group mean bandwidth was 52.98 μ V (SD 27.62). Median peak count in 60 second epochs averaged 3.63 (SD 1.74), while median proportion <10 μ V was 22% (SD 0.20). The group mean of lower border within-subject aggregated medians was 6.20 μ V (SD 2.13). Group mean lower border standard deviation was 3.96 μ V. Proportion <10 μ V showed a strong negative correlation with the natural log of the lower border median ($r = -0.906$, $p < .0001$) after controlling for PMA.

Conclusions—This study introduces a novel quantification process by counting peaks and proportion of time <10 μ V. Expanded definitions and analytic techniques will serve to strengthen

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Conflict of interest statement

All authors declare no conflict of interest.

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the application of existing scoring systems for use in naturalistic research settings and clinical practice.

Keywords

Neonatal Brain Function; Premature Infants; Amplitude-integrated EEG; Limited Channel EEG; aEEG; Neonatal Development; Sleep-wake Cycling

1. Introduction

Clinical and research advances in neonatal neuromonitoring and neuroprotection have grown rapidly in the recent published literature. It remains critical however, to establish methods for monitoring that are well tolerated by vulnerable infants and yield quantifiable information. Amplitude-integrated EEG (aEEG) recordings are processed EEG signal from one or more channels without the specific measures for eye movement, electrocardiography (ECG), or respiratory data that are usually collected in polysomnography or conventional bedside EEG. aEEG signal is derived from the original EEG signal by processing to digitally amplify, smooth, rectify, and compress raw EEG onto a piece-wise logarithmic display (1). The trended signal representing background EEG is then visually assessed with regard to the shape and amplitude level of the signal for patterns reflecting brain function. The reader is referred to the following references for technical details about aEEG and information about clinical uses (2–6).

Brain function patterns vary with maturation, sleep/wake state, or injury, and reflect background brain function over time (1, 6). In particular, aEEG captures the two major background brain function patterns of newborns, continuity and discontinuity, and the cycling that represents a transition from one to the other. Common patterns of the trended image are evaluated in terms of lower and upper border, and the bandwidth or difference between the borders of the graphic image.

Continuity is the pattern of brain function depicted by uninterrupted EEG signal activity, with steady amplitude in a range consistent with gestational development (in the absence of injury, illness, or certain medications). Immaturity and medications such as sedatives and anticonvulsants reduce continuity of the signal and resultant lower border amplitude as reflected by the aEEG (7–13). If the lower border of an aEEG trend is consistently above 5microVolts (μ V), the pattern is generally defined as continuous (1, 6, 14–16). In contrast, discontinuity consists of mixed amplitudes patterned as bursts of high amplitude EEG signal interspersed with near zero amplitude, quiescent intervals. The burst and quiet signal results in an interrupted, less dense graphic aEEG pattern than the image formed by continuity. When trended by aEEG, the less dense discontinuous EEG signal plots graphically as a lower border below 5 μ V (commonly 3–5 μ V) with a simultaneously high upper border. The resulting wide bandwidth between the two borders is a visual classification of discontinuity (1, 6, 14–16). Bursts of amplitude and interrupted signal are hallmarks of premature brain function described for decades (17). Although there is controversy in the literature about the timing of obvious cyclic changes between continuity and discontinuity and the relation to sleep and wake cycles, the first signs of clear cycling between discontinuity and continuity have been documented to emerge as an otherwise healthy infant reaches 29 weeks postmenstrual age (PMA) (18). Continuity, discontinuity, and what is commonly referred to as sleep-wake cycling between the two patterns form the basis of interpretation of aEEG data.

Among healthy premature infants, the brain function signal develops to reflect a primarily discontinuous aEEG pattern early in life with functional maturation to more continuous

signal as the infant approaches term gestation. The pattern changes are aligned with the findings that the background EEG signal occurs as the result of neuronal firing in an oscillatory network between the thalamus and the cortex (19, 20). With maturation brain function becomes more organized and begins to consistently cycle between periods of continuity and discontinuity, which will ultimately reflect developing sleep states.

There is growing support for the use of aEEG in research with premature infants; however, comprehensive interpretation is limited by challenges in reliably quantifying and summarizing these data. While visual qualitative evaluation of aEEG provides meaningful clinical information, quantifiable summary statistics needed for research are not readily available. Classification systems to date rely upon some level of qualitative judgment to determine cycles of continuity and discontinuity, or complex computation of intervals between bursts of amplitude. Alternatively, some researchers use the raw EEG waves that are not amplitude integrated, available from a single or limited channels, then conduct transformations and signal analysis in the frequency domain (21–23). Premature infants characteristically maintain high power in the very low frequency range, which can limit the ability to detect small spectral changes. Assessment of premature infant brain function is further complicated by the well-described maturational changes in EEG and brain function patterns that evolve over the weeks prior to term gestation (10, 18, 24–26). A clear need for quantitative interpretation has continued despite increased interest in the study of brain function by EEG and aEEG (27).

When applying a scoring system originally designed to demonstrate maturation of healthy premature infant brain function(15), we identified challenges of qualitatively assigning categories to emerging patterns of continuity and cyclicity. Visual assessment of aEEG bandwidth on the piecewise logarithmic scale was a major barrier. The categories in the scoring did not provide the level of discrimination needed for our work. As a result, we endeavored to develop quantitative approaches to enhance the interpretation of aEEG signal and further expand the utility of brain function monitoring as a useful measure for future studies involving premature infants. This paper presents a novel approach to analysis of neonatal brain function as measured by amplitude-integrated electroencephalography. The purpose of this exploratory study was to quantify components of premature infant brain function, measured by aEEG. In particular, the aim was to objectively describe variations in the lower border and bandwidth (difference of upper and lower borders) of the aEEG signal and cyclic changes between states evidenced by patterns of continuity and discontinuity.

2. Methods

2.1. Participants

The exploratory design utilized data from two related aEEG projects; one involving stable premature infants and the other involving ill premature infants receiving opioids for sedation or analgesia (opioid outcomes are not reported in this paper). Infants were recruited from two Level III NICUs in the Pacific Northwest region of the U.S. Inclusion criteria for the combined sample were ages 24–42 weeks PMA (calculated by mother's last menstrual cycle and prenatal ultrasound or physical exam [modified Ballard] after delivery if needed), and approval of the NICU medical providers that the infant was medically stable. Infants were excluded if they had known congenital or acquired neurological conditions (grade III or greater intraventricular hemorrhage, periventricular leukomalacia, seizures), were receiving high frequency ventilation, or if their parents were not English speaking. Institutional review board approval was obtained, and parents gave informed consent for participation of their infants.

2.2. Procedure

A single aEEG recording was obtained from each infant while in the NICU without disruption of normal care activities. We used standardized placement of three hydrogel electrodes in the P3–P4 location by 10–20 international system (28) after a standardized protocol for skin preparation (29). Continuous recordings between handling for care-giving or feeding times were obtained to capture expected sleep cycles. Recordings ranged from 1.67 hours to 12.83 hours in length, depending upon the project (opioid or stable premie).

2.3. Instrument

All recordings were made using the Olympic CFM 6000 (Natus Medical, San Carlos, CA). Researchers have established prognostic sensitivity and specificity in both term and premature infants after brain injury for aEEG signals, as recorded by this device and other aEEG devices (4, 16, 30–33). Validity has been demonstrated in comparison with conventional EEG in varied populations (5). EEG signal was sampled 100 times per second. The concurrent raw EEG signal and continuous impedance monitoring enhanced artifact identification and signal fidelity in real time.

2.4. Analysis

Analysis was conducted on the downloaded signal output devised by the manufacturer's algorithm for cerebral function monitoring (CFM) signal. The single channel EEG was automatically filtered and amplitude integrated between 2–15 Hz with a proprietary filter. Upon evaluation of the spectrum of the CFM signal output as generated by the device we found that 98.94% of the power is less than 0.25 Hz, for which the Nyquist sampling rate would be appropriate at 1 sample every two seconds. With further evaluation, we determined that 99.9% of the spectral power would be preserved at a sampling rate of 4 per second. Thus we chose to reduce the 100 data point/second aEEG signal by a time-sampling strategy to four samples per second. We employed a process of block average sampling every 0.25 seconds, this retained a single mean value for each 25 data points, which served to reduce and further slightly smooth the signal. Our intent with this approach was to achieve efficiency of analysis and we then made an ad hoc choice to further block the resulting signal into 60-second epochs across each recording. *See Figure 1. Example of Continuous and Discontinuous Patterns of aEEG Before and After Sampling Strategy was Applied.* Due to the exploratory nature of this study and our interest in evaluating transitions between continuity and discontinuity, data from each infant's entire recording were included.

We designed an empirical program to quantify discontinuity as evidenced by number of peaks in the signal. First, we estimated baseline amplitude by computing a running median over ten seconds of data and we then counted peaks in the amplitude greater than 10 μV above baseline. We also created a calculated variable to measure the proportion of time with amplitude less than 10 μV in each 1 minute block. Peak counts and time measured in percent below 10 μV together provided a preliminary quantification of discontinuity, roughly reflecting the bursts (peaks) and quiescent periods of low amplitude. We chose 10 μV as a strategy for both peak count and estimation of low amplitude intervals between peaks, based on prior published findings (30, 34–36) and after conducting varied explorations of low amplitude periods during our aEEG recordings. We evaluated the sensitivity and distribution of our variables representing proportion of time less than 5, 10, 15, and 20 μV within and across subjects, and found the area under the ROC curves for 5 and 10 μV outperformed the others by several fold. Additionally, we discovered that some of our subjects never demonstrated time at low amplitudes below 5 μV , which skewed the distribution of data and although the higher amplitude thresholds of 15 and 20 μV retained more normally distributed data, these thresholds were not useful to distinguish age groupings that were

included in our convenience sample. Preliminary testing of these data demonstrated that proportion less than 10 μ V showed the strongest relation to minimum values of the lower border as compared to 5, 15, and 20 μ V thresholds. After taking these explorations of the data together, we determined that 10 μ V was the best threshold for our aim of quantifying patterns of discontinuity and emerging periods of continuity. Amount of time with the signal at low amplitude influences the overall amplitude at the lower border as a function of aEEG signal.

Continuity was objectified by the mean and standard deviation of three characteristics: (1) the maximum and (2) minimum aEEG values and (3) a calculated bandwidth value represented by the difference between minimum and maximum for each epoch. Extensive within-subject analyses were conducted to evaluate each of the above variables individually and in combinations to explore quantitative techniques and to generate infant summary measures.

In order to compare data across infants, aggregated values were obtained. Within each subject, median values of the full recording were derived for variables of interest including: CFM maximum, minimum, standard deviation, bandwidth, proportion of time less than 5, 10, 15, and 20 seconds, and the peak count/minute block. Some variables were also natural log transformed prior to calculating the median. The within-subject single median values for each variable were then combined in aggregate to calculate group mean and SD. Across subject analysis (e.g. by PMA) was performed by comparing the aggregated medians across the sample. In general, for within-subject analysis, median values for study variables were chosen to robustly represent each minute of data due to the widely skewed distribution of amplitude and the peak/burst oriented nature of the signal. Group means across subjects are then reported for minimum, bandwidth and standard deviation of aEEG signal derived from the median of each individual subject's full recording.

Although group comparison was not among the study aims, the maturational trajectory of premature infant brain function heavily overlies the patterns and measurements under this inquiry, and the convenience sample reveals a mixed group of early premature and term gestation infants. To that end, we chose to more closely examine differences based on PMA highlighting infants less than 30 weeks of age, who are not expected to have fully developed patterns of continuity in the signal or mature cycling between discontinuous and continuous brain function. Exploration of variables within the data set across maturational groups will give direction for future work.

After visually analyzing the data through plots by variable across the time series, the two calculated variables (peak counts and proportion less than 10 μ V) were correlated with the quantitative measures of lower border and bandwidth. Postmenstrual age (PMA) was controlled when exploring correlations among variables. A subgroup of infants less than 30 weeks PMA ($n = 5$) was analyzed in order to establish quantification of discontinuity in early gestations. The subgroup analysis also served to quantify pattern differentiation representative of early signs of evolving continuity. Signal processing was conducted in MatLab R2011a (The MathWorks, Natick, MA). We then exported files to SPSS ver.15 (SPSS, Chicago, IL) for further visual exploration and statistical comparisons using Student's independent sample t test to test group differences in peak count and time at low amplitude and Pearson's product moment correlation coefficients to test the relation between time at low amplitude and CFM variables of lower border (minimum) and bandwidth (maximum minus minimum) and maturation.

3. Results

Twenty five infants were recruited into the study. Twenty four infants (nine male) who had a mean PMA of 33.11 weeks (SD 3.49), with birth weights ranging from 0.54 to 3.49 kg were included in the analysis. *See* Table 1. Demographic Characteristics of Participating Infants. Infants ranged from 5 days to 6 weeks in age when studied, mean age was 2.62 weeks, or approximately 18 days old at the time of the recording. Data from one infant were not analyzed due to high impedance for greater than 90% of the recording despite repositioning of electrodes. Two infant participants were recruited from a surgical center and were within 48 hours of surgical intervention for gastroschisis at time of recording. These infants were extubated and receiving standard pain management; post anesthetic physiologic effects were not evident. The remainder of the participants had a primary diagnosis of prematurity with respiratory distress. Eight infants received small opioid doses (0.05 mg/kg) during the recordings and were recruited for a separate research aim (not reported here). No sedative agents were administered during the recordings.

3.1. Measures of continuity and discontinuity

3.1.1. Bandwidth—When evaluating bandwidth, less mature infants had wider spread and similar variation in their individual recordings. Group mean bandwidth as aggregated from within-subject medians of all participants was 52.98 μ V (SD 27.62), with individual medians ranging from 17.02 to 101.74 μ V. For the less than 30 week PMA infants, within-subject median bandwidths ranged from 67.51 to 101.74 μ V, group mean 92.56 μ V (SD 14.27).

3.1.2. Proportion less than 10 μ V and peak counts—As previously defined, peak counts and proportion less than 10 μ V were utilized to quantify discontinuity in the sample. Across the sample, median peak count in 60 second epochs averaged 3.63 (SD 1.74), while the median proportion less than 10 μ V was 22% (SD 0.20). Less mature infants had higher peak counts and more time at low voltage. Among the less mature infants of lower gestation (below 30 weeks PMA), median peak count in 60 second epochs ranged from 0–6, mean 4.6 (SD 1.14), while the median proportion less than 10 μ V was 51% (SD 0.17).

3.1.3. Lower border—Quantification of continuity included assessment of lower border voltage and emerging changes in voltage across the recording. Less mature infants had a lower mean voltage for the lower border with limited variation. The aggregated group mean of lower border within-subject medians was 6.20 μ V (SD 2.13), ranging from 2.3–9.43 μ V. The lower border amplitude for the less than 30 week PMA infants ranged from 2.3–4.16 μ V, group mean 3.22 μ V (SD 0.68).

3.2. Measures of cycling

3.2.1. Bandwidth variance—As narrowing bandwidth, with a concurrent increase in lower border, is a sign of increasing continuity, the variance across recordings should reflect emerging cycles between continuous and discontinuous periods of brain function. Our data showed only a slight decrease in variance for the younger infants. For the entire sample, the group's mean of within-subject standard deviation for bandwidth was 24.23 μ V representing fluctuations within each recording. The variance of the within-subject bandwidth for the infants with PMA less than 30 weeks was 23.02 μ V (SD 2.80).

3.2.2. Lower border variance—The aEEG lower border offers the earliest visual clues to cycling, in the form of gentle undulations along the lowest edge. As the periods of continuity lengthen, lower border variance increases. Our data showed a smaller lower border variance for the younger infants. The full sample group mean lower border standard

deviation was $3.96\mu\text{V}$. In contrast, among the infants <30 weeks PMA, the group mean standard deviation of the lower border was $1.65\mu\text{V}$ (SD 0.42).

3.3. Effect of maturation

After plotting the within-subject medians and group aggregated values for each variable, the effect of maturation was apparent upon visual analysis. Within and across subject descriptive analyses revealed expected variations by increasing PMA, including increasing voltage at the lower border and narrowing bandwidth highlighted after 30 weeks PMA. *See Figure 2. Effect of PMA on aEEG Signal Characteristics.* When within-subject EEG bandwidth data were natural log transformed to achieve a more normal distribution, a strong negative correlation was shown with increasing PMA ($r = -0.88$, $p < .0001$) by Pearson two-tailed correlation. Partial correlation to control for PMA retained a moderately strong relation ($r = .69$, $p < .0001$) between peak count and a measure of variance across the recording, log standard deviation aggregated by median for each infant. *See Figure 3. Log Bandwidth (within-subject median) by Postmenstrual Age (PMA).* After controlling for PMA, the proportion of one minute epochs below $10\mu\text{V}$ showed a strong negative correlation with the natural log of the lower border median ($r = -0.906$, $p < .0001$). The lower border of aEEG is affected by the flat signal at low or near zero amplitude interspersed between bursts of high amplitude. Thus the amount of time at low amplitude is expected to relate strongly to lower border values. As the percent of time with low voltage increased, the lower border decreased, in effect reflecting discontinuity of brain function even after removing the effect of age. Higher mean peak counts and proportion below $10\mu\text{V}$ were evident in younger infants. *See Table 2. Descriptive Summaries of Continuity with Comparison by Low PMA (<30 weeks).*

3.4. Other analyses

No differences were noted on the basis of sex, or any other demographic characteristics not associated with maturation.

4. Discussion

Our results demonstrate that discontinuous aEEG patterns can be directly quantified with respect to amplitude peaks and quiescent periods across PMA range of 26 to 40 weeks. Less mature infants had higher proportion of time at low signal amplitude ($<10\mu\text{V}$) with higher peak counts and lower aEEG signal border values which correlated with increasing bandwidth of aEEG signal. As an indication of early cyclicity, we found lower border variance to increase in accordance with maturation.

This study adds to the growing body of literature describing methods to systematically quantify the brain function of premature infants for exploration of varied aspects of neonatal care outcomes (13, 37–40). While feasibility of aEEG is now established among early born infants of low PMA, interpretation has continued to rely upon either complex spectral analysis, proprietary software to calculate interburst intervals, or expert visual pattern analysis. Our study presents a computational method to quantify aEEG, useful in premature infant research.

Similar to the findings reported by the Burdjalov (15) group, our aggregated data reflect the effect of increasing PMA on each of the common aEEG characteristics including: lower border, bandwidth, and presence of cycling between. We found bandwidth (natural log transformed) to be the strongest reflection of maturation, with further delineation between weeks of gestation.

Our initial approach to introduce a process for quantifying discontinuity included the application of the calculated variables: count of peaks $>10 \mu\text{V}$ above baseline and proportion of time (in one minute block) with amplitude $<10 \mu\text{V}$. These variables are conceptually consistent with the work of the Australian group (30), who in their study of premature infants conducted quantitative analysis of EEG (from aEEG) for the purpose of predicting outcome after intraventricular hemorrhage or other neurologic injury, used a cut off value of $<80\%$ at $10 \mu\text{V}$ over a two hour epoch. Percentages of low voltage within the epoch are associated with discontinuity and are known to decrease with maturation (27, 34).

Our data reflected the range of developmental progression within our broad sample (26–40 weeks PMA), which led to examination of findings for the small subgroup ($n=5$) of infants with PMA <30 weeks in our sample. As expected, when averaged across these young infants, peak counts were higher and proportion below $10 \mu\text{V}$ was higher than the means of each for the entire group of mixed gestational ages. Conversely, high peak counts if detected without elevated percent of time below $10 \mu\text{V}$ may signify increasing continuity. *See Table 3. Conceptual Framework for aEEG Interpretation.*

Although our study was not designed to provide standardized values, it may be possible to apply these quantifiable methods to the scoring proposed by the Burdjalov (15) tool, see above for discussion of indicators. The first two indicators of the tool are strictly qualitative, continuity and cycling, requiring expertise or judgments to apply the scoring criteria. Our methods may have value in reducing the reliance on qualitative decisions, in particular for the continuity indicator, although future work is warranted to develop cut points for peak counts and proportion below $10 \mu\text{V}$ to differentiate “somewhat continuous” from either “discontinuous” or “continuous” and to better quantify the emerging process of cycling between. Outside of scoring maturational changes, peak counts and assessment of low voltage proportions may offer useful quantitative approaches to measuring the effect of interventions conducted in the NICU. Neurologic effects of medications and physiologic therapeutics on vulnerable infants raise many research questions that could be informed by measuring brain function. Interventions such as skin to skin holding, developmentally supported positioning, or gentle parent touch are well suited to enhance brain growth and normal development. Brain function patterns would be excellent non-invasive short term outcomes for clinical research. In practice, health care providers may be better prepared to plan care-giving to reduce interruption of sleep states; with brain function monitoring that is quantifiable. Amplitude-integrated EEG data interpretation in the context of optimizing premature infant care-giving will be made more accessible with straightforward techniques to define and gauge both continuity and discontinuity of brain function.

We have keen interest in very young premature infants <30 weeks PMA, who present limited channel signals that are the most difficult to differentiate quantitatively — due to absence of continuity and clear cycling. This led us to look for opportunities to quantify subtle differences in discontinuity, within subject. We believe that emerging segments of continuity were expressed in our data in a combination of higher peak counts coupled with lower proportion of time below $10 \mu\text{V}$. Understanding the functional characteristics of discontinuous signal generated early in gestation and differences in function as the shorter segments seen later during cycling will provide insight into brain development and sleep processes. There are surely complex relations within these patterns that may be best explored using alternative analytic approaches. Some authors recommend nonlinear analyses to better explore the multi-level signals that make up neonatal brain function (27, 41, 42).

We recognize the following limitations of this exploratory work related to instrumentation, analysis, and sampling procedures. Amplitude-integrated signal is obtained from a single channel EEG without the ability to assess focal information including symmetry, synchrony

across hemispheres or detailed frequency (without raw EEG analysis). Further, the development of aEEG algorithms, such as for the CFM 6000 in the adult population with later translation to neonates, especially premature neonates may contribute to difficulties in differentiating subtleties unique to neonatal brain function. However, the non-invasive nature of obtaining aEEG in the NICU and maintaining long recordings over hours are major benefits. Including infants with varied PMA in our study cohort is notably problematic. We were limited by the convenience samples of our naturalistic study design, thus these findings should be considered exploratory and should not be generalized without further testing among homogeneous groups of larger numbers to represent the differences in maturation of brain function patterns.

With the understanding that artifact management is a key aspect of research involving EEG generated signal, we did not approach this exploratory analysis with ardent attention to artifact reduction. There are without doubt issues associated with skin-electrode interface resulting in high impedance, and movement artifact included in our data set. We chose instead to conduct an overview analysis to explore methods to begin quantification of the encompassing patterns of continuity and discontinuity over hours in our full recordings. The recordings are of varied lengths and the use of median aggregates and long (1 minute) blocking may help to ameliorate the effect of artifact within subject by reducing the outlier effect of short bursts of extreme amplitude within each epoch of data. Future studies should more directly address impedance, motion, and behavioral state of the infant (43).

This analysis was limited by our aim to simply quantify and describe the characteristics of continuity and discontinuity. Our peak counting variable was designed upon an empirical process to estimate a baseline (moving median average window). Recognizing that this approach may over or underestimate peaks, we chose it as a starting place for our exploration. Further, our process to estimate proportion less than $10\mu\text{V}$ is not as sophisticated as measuring the intervals between bursts of electrical signal, but our variables do not require agreement of a common definition for bursts among expectedly non-stationary data or extremely short data blocking strategies with resultant computational burden (13, 22, 31, 37).

The small study sample comprised a wide range of developmental ages. This offered opportunities for exploration using a descriptive approach and obvious drawbacks for generalization. The limitations of recruiting vulnerable infants receiving intensive care and a naturalistic design to capture exposure to opioids (not reported here) necessitated expansion of the inclusion criteria to infants closer to term development. Also, the sample did not equally represent sex, only 37.5% of the sample was male. Future studies to further develop or validate quantitative techniques for aEEG interpretation would be best served by purposive sampling of a homogenous group with respect to maturation or resource to obtain a larger sample and conduct more detailed analysis controlling for maturational effects.

In conclusion, these data were examined in order to identify additional strategies for quantification of aEEG signals. Expanded definitions and analytic techniques will serve to strengthen the application of existing scoring systems for use in naturalistic research settings and clinical practice. Our findings indicate that it is possible to make determinations of continuous and discontinuous patterns with straightforward quantifiable measures, and that this approach behaves in accordance with expected maturational changes. Taken together with quantified measures of the lower border and bandwidth of aEEG signal output, counting peaks and estimating proportion below $10\mu\text{V}$ may be useful for future researchers to explain effects of interventions, medications, and brain function disruption related to injury even among infants of gestation less than 30 weeks.

Acknowledgments

Funding:

This work was funded in part by the following: NIH/NINR T32-NR007106 [Thorngate & Foreman], F31-NR011365, NIH/NLM T15LM007442 [Thorngate]

Additional funding sources included: Integra Neuroscience Nurses Foundation, Hyundai Motors Scholar/American Nurses Foundation, Sigma Theta Tau, Psi Chapter [Thorngate]

UW School of Nursing Research & Intramural Funding Program [Foreman]

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a. Continuous Pattern (raw EEG)

b. Discontinuous Pattern (raw EEG)

c. Continuous Pattern (after downsampling and blocking)

d. Discontinuous Pattern (after downsampling and blocking)

Figure 1.

Example of Continuous and Discontinuous Patterns of aEEG Before and After Sampling Strategy was Applied

Note. Single infant 34.3 weeks postmenstrual age, 1.65kg,

100 seconds of signal from segment of continuity (a), and discontinuity (b) raw aEEG signal before processing (100 samples/second); and same segments continuity (c), and discontinuity (d) after downsampling by 25% to 4 samples/second, shows effect of smoothing without loss of peaks. See longer and more frequent blocks of data points (time) below $10\mu\text{V}$ in discontinuous segment (interspersed between high peaks) as compared to continuous segment; also number of visible peaks is greater in continuous segment. x axis is signal over time (data points), y axis is amplitude in μV

Figure 2.

Effect of Postmenstrual Age (PMA) on aEEG Signal Characteristics

Effect of postmenstrual age (PMA) on amplitude-integrated EEG (aEEG) Signal Characteristics. y axis is natural log transformed to better reflect distribution of bandwidth values.

Figure 3.

Log Bandwidth (within-subject median) by Postmenstrual Age (PMA)

Natural log transformed aEEG Bandwidth (within-subject median) by Postmenstrual Age (PMA). Each dot represents the median log Bandwidth for an individual infant (N=24).

There is a separation between the younger (<30 weeks PMA) and older (>30 weeks PMA) infants.

Table 1

Demographic Characteristics of Participating Infants (n = 24)

Characteristic	Median	Minimum	Maximum
Age (weeks)			
GA	30.71	24.00	38.50
PMA	33.71	25.71	39.71
Weight at birth (kg)	1.14	0.54	3.49
Weight at time of study (kg)	1.59	0.62	3.49
Intravenous Morphine (n=8)			
Study dose (mg/kg)	0.05	0.03	0.08
Total (mg/kg)	0.41	0.10	3.19
Female (n=15)			

Note. GA = gestational age; PMA = postmenstrual age;

8 infants received morphine doses during aEEG recordings

Total morphine dose includes previous infusions and bolus doses to date

Table 2

Descriptive Summaries of Continuity with Comparison by PMA

Characteristic	All Ages n=24		Infants <30 weeks PMA n=5		Infants >30 weeks PMA n=19	
	Mean	SD	Mean	SD	Mean	SD
Peak Count (number) *	3.83	1.53	4.65	0.94	3.37	1.80
Proportion less than 10µV (%) *	0.24	0.17	0.48	0.13	0.14	0.13
Lower Border (µV) *	6.19	2.13	3.22	0.68	6.97	1.62
Lower Border Variance (µV) **	3.96	3.15	1.65	0.42	4.57	3.28
Bandwidth (µV) *	52.96	27.62	92.56	14.27	42.56	19.48

Note. PMA = postmenstrual age

* group mean calculated from within-subject aggregated medians

** group mean standard deviation of signal from within-subject aggregated medians

Table 3

Conceptual Framework for aEEG Interpretation

Brain Function Pattern	Operational Variables	Derived by	Definition by Key Characteristics	Developmental Changes
Discontinuity	Bandwidth	Difference between aEEG max and min	Wide bandwidth	<i>Initial pattern of very early gestation typical pattern at <30 weeks PMA</i>
	Proportion less than 10 μ V	% of each minute <10 μ V amplitude	Bursts of high amplitude interspersed with low amplitude “quiescent intervals”	
	Peak count	Each point 10 μ V over baseline	Lower number of peaks per epoch	<i>After 29–30 weeks PMA, pattern alternates with continuity and becomes a precursor to quiet sleep</i>
	Lower border	aEEG min Standard deviation of aEEG min	Lower border 3–5 μ V Lower border near flat or with low variance across recording	
Continuity	Bandwidth	Difference between aEEG max and min	Narrow bandwidth	<i>Develops over time, usually seen by 29 weeks PMA</i>
	Proportion less than 10 μ V	% of each minute <10 μ V amplitude	Dense frequency of steady amplitude	<i>When alternating with discontinuity is considered to be active sleep or awake</i>
	Peak count	Each point 10 μ V over baseline	Higher number of peaks per epoch	
	Lower border	aEEG min Standard deviation of aEEG min	Lower border >5 μ V Lower border shows variance across recording	<i>Pattern may regress to discontinuity after injury or medication</i>
Cycling	Bandwidth variance across recording	Standard deviation of bandwidth	Change between discontinuity and continuity in the same recording	<i>Initially presents as slight variation in lower border visible as early as 25–26 weeks PMA</i>
	Lower border variance across recording	Standard deviation of aEEG min		<i>Progresses to smooth cycles by term, quiet sleep 20 minutes</i>

Note. PMA = Postmenstrual Age, aEEG=amplitude-integrated EEG, Min=Signal minimum, Max=Signal maximum