Early Human Development 89 (2013) 931–937

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Quantification of neonatal amplitude-integrated EEG patterns ☆

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ARTICLE INFO

Article history:
Received 24 January 2013
Received in revised form 14 September 2013
Accepted 24 September 2013

Keywords:
Neonatal brain function
Premature infants
Amplitude-integrated EEG
Limited channel EEG
aEEG
Neonatal development
Sleep-wake cycling

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) of 33.11 weeks (SD 3.49), average age of 2.62 weeks (SD 1.35) and mean birth weights of 1.39 kg (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 μV, and peak counts. Variance of bandwidth and lower border denoted cycling.
Results: Group mean bandwidth was 52.98 μV (SD 27.62). Median peak count in 60 second epochs averaged 3.63 (SD 1.74), while median proportion <10 μV was 22% (SD 0.20). The group mean of lower border within-subject aggregated medians was 6.20 μV (SD 2.13). Group mean lower border standard deviation was 3.96 μV. Proportion <10 μV 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 μV. Expanded definitions and analytic techniques will serve to strengthen the application of existing scoring systems for use in naturalistic research settings and clinical practice.

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

☆ 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]. The authors acknowledge the support of Robert L. Burr PhD, MSEE, Office of Nursing Research, University of Washington.
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http://dx.doi.org/10.1016/j.earlhumdev.2013.09.018

aEEG trend is consistently above 5microVolts (μV), 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 result 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 μV (commonly 3–5 μV) 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 the 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 caregiving or feeding times were obtained to capture expected sleep cycles. Recordings ranged from 1.67 h to 12.83 h 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 and 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 2 s. 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 s, 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 Fig. 1. 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