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Characterization of neonatal seizures by conventional EEG and single-channel EEG ☆

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Abstract

Objective: To perform a detailed, contemporary temporal–spatial characterization of neonatal seizures (NS) and to compare conventional EEG (CEEG) to single-channel EEG for NS detection.
Methods: Digitally recorded CEEGs were reviewed for NS characteristics (quantity, duration, location of onset, peak-to-peak amplitude). The presence and characteristics of each NS were simultaneously noted in a single, derived EEG channel ($C_3 \rightarrow C_4$).
Results: Eight hundred fifty-one seizures from 125 CEEGs recorded were analyzed. Mean seizure rate was 7.0 NS/h (range: 0.5–21). Mean seizure burden (percent time CEEG showed NS at any location) was 24.8% (range: 0.7–86.9). Seizure rate was only moderately correlated with seizure burden (Spearman coefficient = 0.58). Eighty-one percent of NS originated from central–temporal or midline vertex electrodes. Seventy-eight percent of NS appeared in the $C_3 \rightarrow C_4$ channel.
Conclusions: Accurate measurement of NS burden requires detailed temporal–spatial characterization. The theoretical ceiling of sensitivity for NS detection in the single EEG channel $C_3 \rightarrow C_4$ is high. However, further processing the raw EEG in limited electrode arrays may reduce the sensitivity of NS detection.
Significance: CEEG is the gold standard for NS detection. However, reduced montage EEG techniques are increasingly available. This detailed contemporary temporal–spatial characterization of NS evaluates the potential limitations of reduced montage techniques.

Keywords: Neonatal seizures; Neonatal EEG; Amplitude-integrated EEG; Cerebral function monitor

1. Introduction

Neonatal seizures occur in 1.5–3.5 per 1000 live term births (Eriksson and Zetterstrom, 1979; Lanska et al., 1995; Ronen et al., 1999). Usually, neonatal seizures are symptomatic of an acute illness such as stroke, hypoxic ischemic encephalopathy (HIE), or infection. Neonates who have seizures are at high risk for death or significant neurological disability (Scher et al., 1989; McBride et al., 2000; Rutten et al., 2002). Based on animal and limited human data, it is believed that electrographic seizures themselves may contribute to adverse neurodevelopmental outcomes (Liu et al., 1999, 2003; Rutten et al., 2002).

Because most neonatal seizures are subclinical (Bye and Flanagan, 1995; Clancy et al., 1998), electrographic confirmation is required for their diagnosis and accurate quantification. Conventional EEG (CEEG) using the international 10–20 system, modified for neonates, is the gold standard for neonatal seizure detection. However, CEEG is not always available. Therefore, in an attempt to detect seizures early in the high risk neonate's course, automated seizure detection algorithms and limited array cerebral function monitors have been introduced in some

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neonatal intensive care units (Gotman et al., 1997; Navakatikyan et al., 2006; Lommen et al., 2007).

Amplitude-integrated EEG (aEEG) is among the most commonly employed methods of cerebral function monitoring and seizure detection in the neonate. These instruments are intended to be applied and interpreted at the bedside by neonatologists. Typical aEEG uses a single EEG channel with biparietal electrodes ($P_3 \rightarrow P_4$) to monitor the EEG background in a limited area of the neonate's brain (Hellström-Westas et al., 2006). The $P_3 \rightarrow P_4$ location was selected because it overlies the apex of the cerebrovascular watershed zone (Hellström-Westas et al., 2003). EEG background activity recorded by aEEG is reported to correlate well with conventional neonatal EEG (Hellström-Westas et al., 1995; al Naqeeb et al., 1999; Toet et al., 2002). Some electrographic seizures can also be detected by distinctive patterns of change in the aEEG signal (Toet et al., 2002; Naqvi et al., 2004; Rennie et al., 2004). However, the sensitivity and specificity of single-channel raw EEG recording for seizure detection by aEEG or other algorithm-based signal processing methods are unknown. Furthermore, potential factors that might influence single-channel neonatal seizure detection, such as seizure duration, rate, and amplitude, have not been quantitatively described.

The purpose of this study is to characterize a large number of contemporary electrographic neonatal seizures using CEEG and to determine which seizures are present in a single derived EEG channel, $C_3 \rightarrow C_4$, analogous to that used to create aEEG. This allows comparison between seizure characteristics on conventional EEG and a single EEG channel ($C_3 \rightarrow C_4$), as well as to determine the theoretical maximum sensitivity of electrographic seizure detection by aEEG or other algorithms.

2. Methods

We reviewed a convenience sample of neonatal CEEGs with electrographic seizures that were recorded as part of prior research protocols or for clinical purposes. Patient characteristics, including gender, estimated gestational age (EGA), and conceptional age (CA), were recorded, when available. CA was determined by adding the legal age to the EGA. Our hospital's Institutional Review Board approved this study.

For uniformity, all CEEG traces were converted to Persyst format (Persyst Corp, Rochester, MN). Each EEG was interpreted by two electroencephalographers and consensus was reached regarding the characteristics in question. An assessment of the CEEG background was made according to a published classification system (Clancy et al., 2003). The onset and termination of each seizure were electronically marked and the duration of each seizure was recorded in a database. When simultaneous independent seizures occurred, they were grouped as one seizure (seizure onset at the beginning of the first ictal pattern and termination at the end of the last ictal pattern), since this is what would be detected in a single EEG channel montage. The maximal ictal peak-to-peak amplitude was measured electronically and was compared to the median interictal peak-to-peak amplitude for each CEEG.

An electrographic seizure was defined as a sudden, repetitive, evolving and stereotyped ictal pattern with a clear beginning, middle, and ending and a minimum duration of 10 s. To be counted as different events, individual seizures had to be separated by at least 10 s.

We digitally created a new single channel, $C_3 \rightarrow C_4$, to represent the raw EEG from which a typical neonatal aEEG would be derived (Fig. 1). All of the CEEG tracings were recorded referentially using referential digital amplifiers. Recording in this manner allows the re-montaging of channels, either for display or for analysis. To compute the $C_3 \rightarrow C_4$ channel, the stored channel "C4-REF" was subtracted from "C3-REF" for each recording using Matlab data analysis software. No pre-processing (i.e. filtering) was performed on the data. The $C_3 \rightarrow C_4$ channel is spatially very close to the biparietal ($P_3 \rightarrow P_4$) channel that is classically recommended for aEEG. In a typical term infant, C_3 is only about 4 cm anterior to P_3. Thus, there

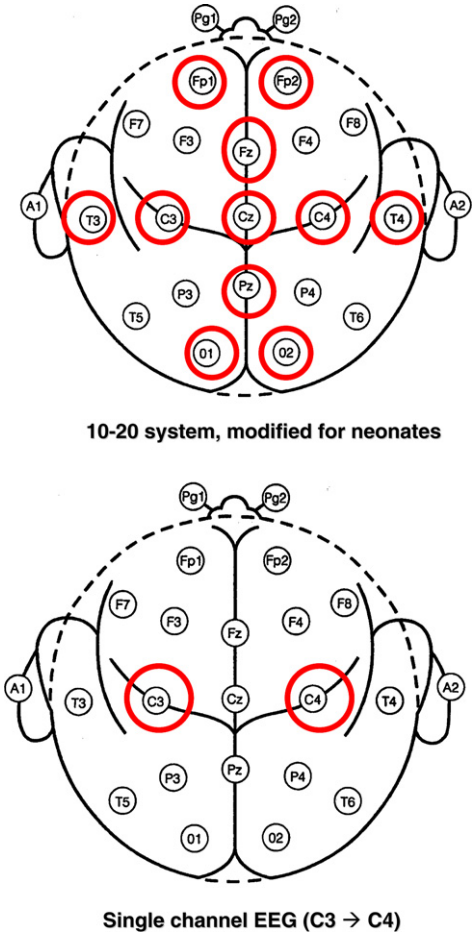

Fig. 1. Electrode placement for the conventional EEG (international 10–20 system, modified for neonates) and for the single channel EEG.

is little chance of error resulting from substituting $C_3 \rightarrow C_4$ for $P_3 \rightarrow P_4$.

The $C_3 \rightarrow C_4$ channel was displayed immediately below the CEEG. For each CEEG electrographic seizure, a determination was made as to whether the ictal pattern was simultaneously detectable in the $C_3 \rightarrow C_4$ channel (Fig. 2). This allowed us to use the visual reinforcement of detecting seizures in the CEEG to maximize the likelihood of detecting the seizures in $C_3 \rightarrow C_4$, but precluded a blinded recording of false positive seizure detections in this channel. We measured seizure duration and the maximal peak-to-peak amplitude in $C_3 \rightarrow C_4$ during each seizure. The ratios of ictal to interictal peak-to-peak amplitude for seizures in this channel were also calculated.

This study was powered to obtain a 95% confidence interval of ±5% around the true percentage of seizures detected with single-channel EEG compared to CEEG. Continuous variables were compared using two-tailed Student's *t*-test. Categorical variables were compared using chi-squared statistics. Correlation between the non-parametric continuous variables (seizure count per hour and seizure burden) was computed with the Spearman coefficient. *p*-Values less than 0.05 were considered statistically significant.

3. Results

This study included 125 CEEGs recorded from 121 infants whose CAs at the time of the EEG recording were 34–50 weeks. Incomplete EGA/CA data were available for 35 subjects obtained from a previous research protocol which included only infants with CA 36–44 weeks. The CEEGs were 23–145 min in duration.

Fifteen percent (19/125) of the CEEGs had normal backgrounds and 23% (29/125) were classified as mildly abnormal. Sixty-two percent of the CEEGs had significant

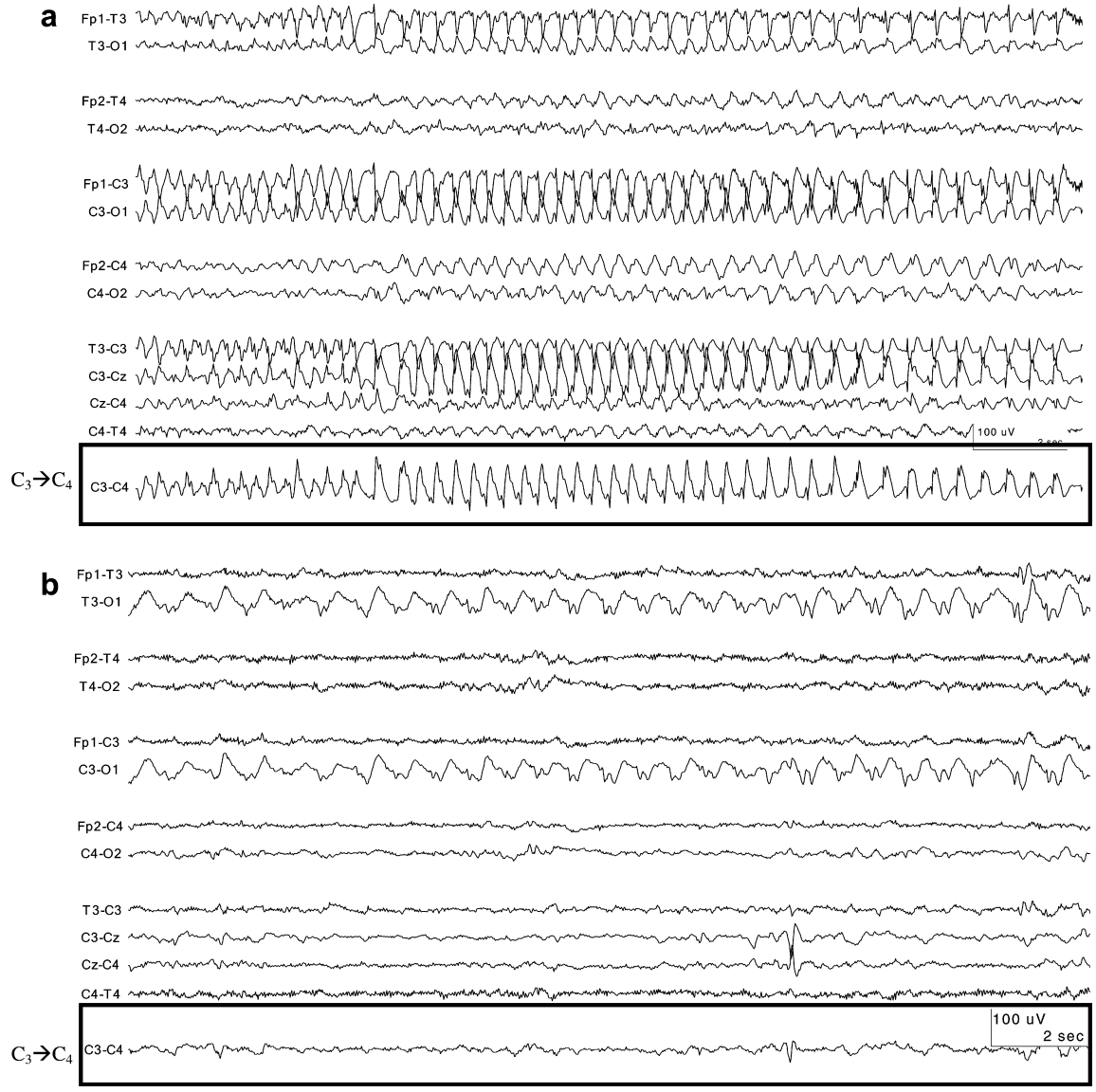

Fig. 2. Examples of neonatal seizures on conventional EEG which are (a) and are not (b) visible in the single $C_3 \rightarrow C_4$ channel.

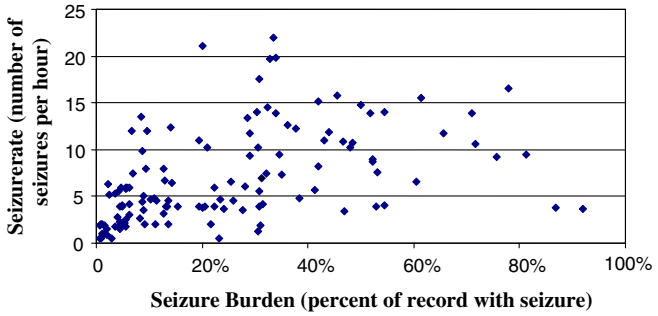

Fig. 3. Seizure burden and seizure rate are only moderately correlated (Spearman coefficient = 0.58).

background abnormalities, classified as moderate (32%; 40/125) or severe (30%; 37/125).

There were 851 seizures, with a mean seizure duration of 132 s (range: 10–2314). Mean seizure burden (defined as the percent of the EEG record with ictal activity at any location) was 24.8% (range: 0.7–86.9%). Seizure burden had only a moderate correlation with the seizure rate (mean 7.0 seizures per hour, range 0.5–21; Spearman coefficient = 0.58; Fig. 3).

The distribution of site of seizure origin is displayed in Table 1. Eighty-one percent of all seizures (691/851) originated in either the central, temporal, or midline vertex electrodes. In 36% (45/125) of the CEEG records, every seizure originated from the same location (unifocal). The seizure onset was unihemispheric, with all seizures beginning in one hemisphere, in 54% (67/125; includes unifocal records). Seizures were multifocal in onset (within one CEEG there were three or more locations of seizure origin, including independent onset from both hemispheres) in 34% (42/125).

The quantitative comparisons between measures of CEEG seizures and $C_3 \rightarrow C_4$ seizures are outlined in Table 2. Seventy-eight percent (664/851) of all seizures were visible in the $C_3 \rightarrow C_4$ channel and 94% (118/125) of the records had at least one seizure visible in this single channel. Seizures were significantly briefer in the single channel than in CEEG ($p < 0.001$). This led to a lower detection of status epilepticus, defined as greater than 50% of the tracing with seizures (Ortibus et al., 1998), in $C_3 \rightarrow C_4$ traces (7/125, 6%) than in the CEEGs (17/125, 14%; $p = 0.038$). Seizures were also lower in amplitude in $C_3 \rightarrow C_4$ than in the CEEGs ($p = <0.001$). However, the ratio of ictal to interictal peak-to-peak amplitude in CEEG (2.27 ± 2.14 μV) was not different from the ratio calculated for the single $C_3 \rightarrow C_4$ channel (2.19 ± 1.82 μV; $p = 0.47$).

4. Discussion

This is the largest contemporary study of the temporal–spatial characteristics of electrographic neonatal seizures. To our knowledge, it is also the first to compare neonatal seizures on CEEG to those detected simultaneously on a single EEG channel. Despite significant advances in neonatal intensive care, such as the use of extra-corporeal membrane oxygenation (which exposes newborns to potentially new patterns of cerebral injury) and the routine administration of anxiolytic agents such as lorazepam for agitation (which potentially alters seizure occurrence or characteristics), the temporal and spatial characteristics of neonatal seizures have not changed over the last 20 years. We show here that neonatal seizures remain numerous, but are generally brief, and that seizure burden is formidable in this population of neonates. These findings are consistent with prior studies by Clancy and Legido (1987), Scher et al. (1993), and Ortibus et al. (1998), who reported mean seizure durations of 128–274 s and seizure burdens of 22–40%. The spatial distribution of neonatal seizures has also remained consistent over the years. The majority of seizures in our study originate from central and temporal electrodes. These results echo those of Fischer and Clancy (1987), Helmers et al. (1997) and Patrizi et al. (2003), but are perhaps more relevant now if CEEG will be augmented by monitoring techniques such as aEEG, which use a significantly reduced recording montage.

These details provide an analytical basis for the evaluation of a reduced EEG montage technique, using a single channel derived from $C_3 \rightarrow C_4$. To our knowledge, no prior study has illustrated the characteristics of the raw $C_3 \rightarrow C_4$ EEG for neonatal seizure detection. It is reasonable to expect decreased seizure detection with a reduction of recording electrodes. Others have shown significant declines in sensitivity when evaluating 4 and 9 channel montages compared to CEEG for neonatal seizure detection (Bye and Flanagan, 1995; Tekgul et al., 2005). Nevertheless, the theoretical ceiling on sensitivity for neonatal seizure detection in our single central channel was high, with 94% of EEG records having at least one seizure detected in $C_3 \rightarrow C_4$ and 78% of individual seizures appearing in this single channel. The design of our study may bias the results toward increased seizure detection in $C_3 \rightarrow C_4$, since the seizures were first detected by CEEG. Seizures were briefer and lower in amplitude in $C_3 \rightarrow C_4$ than in CEEG and it is likely that further signal processing will reduce the seizure detection rate by aEEG or other seizure detection algorithms.

Table 1
Distribution of location of seizure onset

Location of seizure onset	Conventional EEG ($N = 851$)	Number of seizures detected in $C_3 \rightarrow C_4$[a] ($N = 664$)	Percent of seizures detected in $C_3 \rightarrow C_4$ (%)
Frontal (FP1/FP2)	39 (5%)	18	46
Central (C3/C4/CZ)	478 (56%)	431	90
Temporal (T3/T4)	213 (25%)	164	77
Occipital (O1/O2)	121 (14%)	51	42

[a] Chi-squared: $p \leqslant 0.001$ for distribution of origin of the seizures detected in $C_3 \rightarrow C_4$.

Table 2
Quantitative seizure characteristics and comparisons between conventional and single channel EEG

	Conventional EEG	$C_3 \rightarrow C_4$	p-Value
Seizures detected	$N = 851$	$N = 664$ (78%)	N/A
Mean seizure duration (s)	132 (10–2314)	100 (10–2313)	$p \leqslant 0.001$[b]
Mean ictal peak-to-peak amplitude (μV)	145 (13–1166)	111 (5–739)	$p \leqslant 0.001$[b]
Mean ratio of ictal to interictal peak-to-peak amplitude (μV)	2.19 (0.5–27.1)	2.27 (0.4–33.8)	$p = 0.47$[b]
Mean seizure burden (percent record with seizure)	24.8%[c] (0.7–86.9)	17.6% (0–18.0)	$p = 0.004$[b]
Mean seizures per hour	7.0[c] (0.5–21)	5.2 (0–18)	$p = 0.003$[b]
Status epilepticus[d]	17/125 (14%)	7/125 (6%)	$p = 0.038$[a]

[a] Chi-squared.
[b] Student's t-test.
[c] There is only a moderate correlation (Spearman coefficient = 0.58) between the number of seizures per hour and the seizure burden.
[d] Status epilepticus was defined as greater than 50% of the tracing with seizures.

A typical aEEG is displayed at a paper speed of 6 cm/h. Therefore, the average electrographic seizure detected in $C_3 \rightarrow C_4$, which lasted 100 s, would correspond to a deflection of 1.4 mm on an aEEG trace. Since the *median* duration of $C_3 \rightarrow C_4$ seizures in this study was 44 s, half of the seizures in our study would be represented by an aEEG deflection of just 0.73 mm or less. Detecting a seizure within an aEEG tracing also requires the seizure amplitude to be conspicuously higher than the EEG background. The ratio of ictal to interictal peak-to-peak EEG amplitudes in our study was approximately 2:1. For some seizures, this may prove to be too low to produce consistently discernible deflections on the aEEG, especially if the deflections are also of short duration. It should also be noted that in practice, many neonatologists place the single channel recording electrodes anteriorly, in order to more easily secure them on the hairless forehead. Since only five percent of seizures in this study originated in the frontopolar electrodes, this practice could also lower the sensitivity of neonatal seizure detection by single channel EEG. Clearly, all of these factors will challenge the ability of a neonatologist to detect electrographic seizures in clinical practice.

Nevertheless, single-channel EEG devices do serve an important role in neonatal intensive care. Since aEEG is designed to be applied and interpreted at the bedside by neonatologists, results can be obtained quickly. This can allow for easier and earlier access to basic EEG background data and limited seizure detection. Having prolonged aEEG monitoring may enhance the interpreter's ability to detect some neonatal seizures, compared to simple visual inspection of the patient. However, we have shown here that simple seizure counts do not provide an accurate representation of seizure burden. CEEG remains the gold standard for neonatal seizure detection and for quantification of seizure burden. Seizure detection may be assisted by aEEG or seizure detection algorithms, but detailed measures of seizure quantification will require visual readings of CEEG. Such labor-intensive seizure burden characterization may be required for detailed research studies of antiepileptic drug efficacy and in understanding the relationship between seizure burden and long-term neurodevelopmental outcome, including the development of postnatal epilepsy.

5. Conclusions

The burden of neonatal seizures in critically ill newborns remains high. Neonatal seizures are frequent, but brief, and their average amplitude is only twice that of the interictal background. The theoretical ceiling of neonatal seizure detection by a single raw EEG channel ($C_3 \rightarrow C_4$) is high. However, because the seizures are briefer and lower in amplitude in this single channel, further processing of the EEG to create an aEEG trace will likely significantly reduce its sensitivity for neonatal seizure detection.

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