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# Sensitivity of Amplitude-Integrated Electroencephalography for Neonatal Seizure Detection

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## ABSTRACT

**BACKGROUND.** Conventional electroencephalography remains the gold standard for the diagnosis and quantification of neonatal seizures. However, amplitude-integrated electroencephalography (aEEG) is being introduced to neonatal intensive care as an adjunct for neonatal seizure detection.

**OBJECTIVES.** This study's purpose was to determine the sensitivity of neonatal seizure detection in a single electroencephalogram channel ( $C_3 \rightarrow C_4$ ), used to simulate the raw signal from which aEEG is derived. We also aimed to determine the sensitivity of seizure detection by neonatologists by using aEEG and to establish those neonatal seizure characteristics that are associated with their correct detection by aEEG.

**METHODS.** Conventional electroencephalograms with neonatal seizures were reviewed for electroencephalogram background and neonatal seizure characteristics (site of onset, duration, and peak-to-peak amplitude). The presence, duration, and peak-to-peak amplitude of each seizure were simultaneously noted in a single electroencephalogram channel ( $C_3 \rightarrow C_4$ ). aEEGs generated from this channel were reviewed for background and seizures by 6 neonatologists with varying aEEG interpretation expertise.

**RESULTS.** A total of 851 neonatal seizures from 125 conventional electroencephalograms were analyzed. The patients' conceptional ages were 34 to 50 weeks. Because 94% of the conventional electroencephalograms had  $\geq 1$  neonatal seizure visible in  $C_3 \rightarrow C_4$ , and 78% of all neonatal seizures appeared in the  $C_3 \rightarrow C_4$  channel, the theoretical sensitivity of seizure detection in a single electroencephalogram channel was high. However, seizures were briefer and lower in amplitude in  $C_3 \rightarrow C_4$  compared with conventional electroencephalography. Neonatologists identified seizures in 22% to 57% of the 125 records of neonatal seizure. They detected 12% to 38% of the 851 individual seizures. Multivariate analysis revealed that the appearance of seizures in  $C_3 \rightarrow C_4$ , neonatal seizure duration, seizure amplitude, seizure count per hour, and neonatologists' experience with aEEG interpretation all correlated with neonatal seizure detection.

**CONCLUSIONS.** Even among physicians who have extensive experience, many neonatal seizures are difficult to detect on an aEEG, especially when they are infrequent, brief, or of low amplitude.

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### Key Words

neonatal seizures, neonatal EEG, amplitude-integrated EEG, cerebral function monitor

### Abbreviations

EEG—electroencephalogram  
aEEG—amplitude-integrated electroencephalogram

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**C**LINICAL NEONATAL SEIZURES are diagnosed in 1.5 to 3.5 per 1000 live term births.<sup>1-3</sup> Neonates who have seizures are at high risk for death or significant neurologic disability.<sup>4,5</sup> On the basis of animal and limited human data, it is also believed that the corresponding electrographic seizures have an inherent adverse effect on neonates' neurodevelopmental outcome.<sup>6-8</sup>

Because neonates with seizures are at such high risk for mortality and neurodevelopmental abnormalities, neonatologists and neurologists have great interest in their early and accurate detection. In clinical practice, neonates at high risk for seizures are visually monitored for clinical signs of seizures. When there is a clinical suspicion of seizures, a routine electroencephalogram (EEG) is obtained, and empiric treatment is often administered. This approach presumes that most electrographic seizures give rise to visually observable clinical seizures. However, the majority of electrographic neonatal seizures are subclinical.<sup>5,9-11</sup> Therefore, continuous EEG monitoring is required for prompt and reliable electrographic seizure detection.

In an attempt to identify electrographic seizures early in an at-risk neonate's course, cerebral function monitors, such as amplitude-integrated EEGs (aEEGs), have been introduced in many NICUs. The device uses a single EEG channel with biparietal electrodes ( $P_3 \rightarrow P_4$ ) to monitor the EEG background and to detect seizures.<sup>12</sup> The raw signal is highly filtered, processed, and compressed to display the envelope of lower and upper amplitudes of the EEG signal over time. The electrical background recorded by aEEG is reported to correlate well with conventional neonatal EEG.<sup>13-15</sup> However, because few studies have adequately addressed this question,<sup>15,16</sup> it is not yet clear how sensitive or specific aEEG is for electrographic seizure detection.

The purpose of this study was to characterize a large number of contemporary electrographic neonatal seizures by conventional EEG and to determine the sensitivity of neonatal seizure detection in a single EEG channel ( $C_3 \rightarrow C_4$ ), used to simulate the raw signal from which aEEG is derived. We then examined the sensitivity of electrographic seizure detection by neonatologists using aEEG and sought to identify those seizure characteristics that were significantly associated with their detection by aEEG.

## METHODS

The Children's Hospital of Philadelphia's institutional review board approved this study. We studied a convenience sample of conventional neonatal EEGs with electrographic seizures that were recorded in our hospital from near-term neonates as part of previous neonatal seizure research protocols or for clinical purposes. The EEGs were stripped of patient identifiers and were converted to Persyst format (Persyst Corp, Rochester, MN), which allowed quantitative measurement of some EEG

parameters (eg, peak-to-peak amplitude). Conceptional ages were recorded, when available.

Each conventional EEG was interpreted by 2 pediatric electroencephalographers (Drs Shellhaas and Clancy). Individual records were classified as having a normal or mildly, moderately, or markedly abnormal background, according to a standard classification system.<sup>17</sup> An electrographic seizure was defined as a sudden, repetitive, evolving, and stereotyped ictal pattern with a clear beginning, middle, and ending, an amplitude of  $\geq 2 \mu V$ , and a minimum duration of 10 seconds. To be counted as separate events, individual seizures had to be separated by a minimum of 10 seconds. Seizure onset and termination times, duration, electrode of onset, and maximal peak-to-peak amplitude were recorded.

A new EEG channel,  $C_3 \rightarrow C_4$ , was created to represent the raw data from which an aEEG would be derived. Historically, aEEG leads are placed by neonatologists over the biparietal region ( $P_3 \rightarrow P_4$ ), the apex of the vascular watershed area. Because the locations of  $P_3 \rightarrow P_4$  are not included in the international 10-20 system of electrode placement, modified for neonates, we chose their closest neighbors ( $C_3 \rightarrow C_4$ ), to create a single-channel raw EEG from which the aEEG traces would be derived (Fig 1). In a typical term infant,  $C_3$  is only  $\sim 4$  cm anterior to  $P_3$ . Thus, there is little chance of error resulting from substituting  $C_3 \rightarrow C_4$  for  $P_3 \rightarrow P_4$ .

For each electrographic seizure identified on conventional EEG, we first determined whether the ictal pattern was simultaneously visible in the raw EEG of the  $C_3 \rightarrow C_4$  channel. For each seizure, the electrode where the seizure originated and the times of seizure onset and termination in both the conventional EEG and the  $C_3 \rightarrow C_4$  channel were recorded, as was the maximal ictal peak-to-peak amplitude. The interictal peak-to-peak amplitude was also measured for both the conventional EEG and the  $C_3 \rightarrow C_4$  channel, and the ratio of ictal to interictal amplitudes was calculated for each seizure.

Finally, the single-channel raw EEG recordings were converted to aEEG traces. The durations of the conventional EEG, single channel EEG, and aEEG recordings were identical, because the latter 2 were derived directly from the original EEG traces. The aEEGs were interpreted by 6 neonatologists with varying aEEG interpretation expertise. All had  $\geq 1$  year of experience with aEEG, and 2 were internationally recognized experts. They each received written instructions and a packet of 144 paper aEEG traces. They were informed that some aEEGs contained seizures but others did not. The collection contained 125 records with seizures, which were randomly interspersed with 19 aEEGs without seizures. The neonatologists were asked to (1) score the technical quality of the tracings, (2) classify the aEEG background, and (3) mark with a pen the onset (O) and termination (T) of all portions of the aEEG traces that they believed represented electrographic seizures (Fig 2). The raw

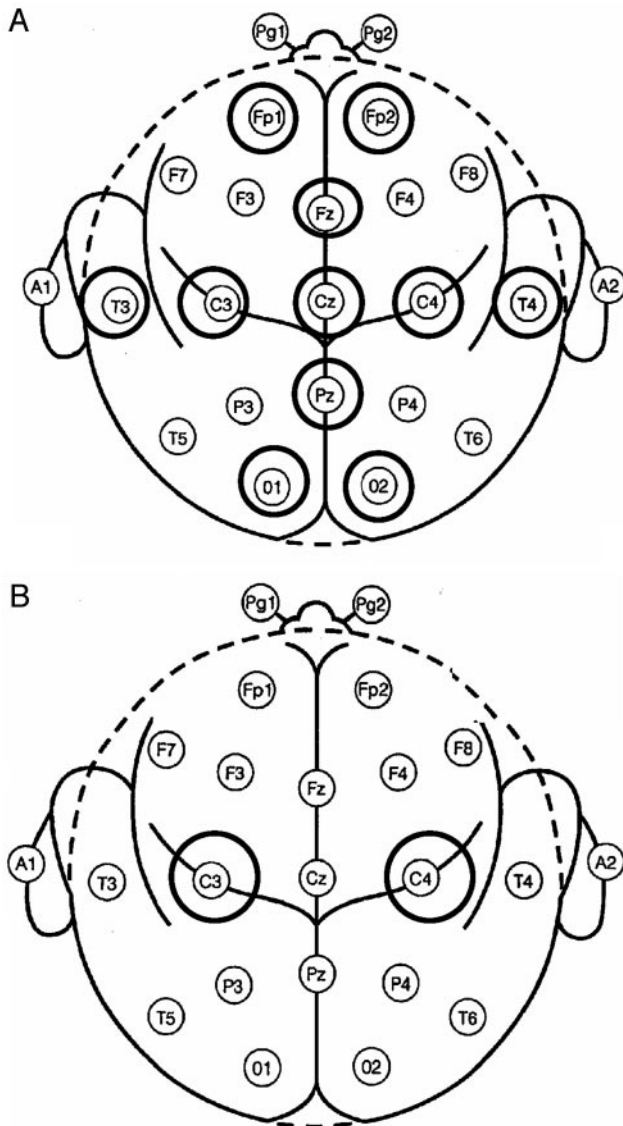


FIGURE 1  
Electrode placement for conventional EEG. A, 10–20 system, modified for neonates. B, Single-channel EEG ( $C_3 \rightarrow C_4$ ).

EEGs were not made available to the neonatologists. In clinical practice, most modern aEEG equipment can call up and display the single-channel raw EEG if requested by the aEEG interpreter. Therefore, the participating neonatologists were instructed to mark the areas of the aEEG traces that would raise their suspicion for a seizure and, consequently, would have triggered them to look at those sections of raw EEG traces had they been available.

Assuming that each conventional EEG would contain 3 electrographic seizures, a power analysis yielded a sample size of 125 EEGs, calculated to obtain a 95% confidence interval of  $\pm 5\%$  around the true percentage of seizures detectable with aEEG. However, because there were more seizures per record than initially estimated, the confidence interval was actually  $\pm 3.37\%$ . Continuous variables were

compared using 2-tailed Student's *t* tests.  $\chi^2$  statistics were used to compare categorical variables. Multivariate analysis was performed using generalized estimating equation with binary outcome (Stata 8; Stata Corp, College Station, TX).<sup>18,19</sup> Variables examined in the model included the seizure's visibility in  $C_3 \rightarrow C_4$ , seizure duration (seconds), number of seizures per hour, location of seizure onset, conventional EEG background classification, ictal peak-to-peak amplitude (microvolts), and the neonatologist's level of expertise in aEEG interpretation. A *P* value of  $<.05$  was considered to be statistically significant.

## RESULTS

There were 851 seizures detected in 125 conventional EEGs obtained from 121 neonates. At the time of their EEG examinations, the patients' conceptional ages (determined by adding the estimated gestation age to the legal age or age since birth) ranged from 34 to 50 weeks. Nineteen control records, without seizures, were also included. Conceptional age were unavailable for 35 infants, whose EEGs were obtained from a previous neonatal seizure research protocol with an inclusion criterion of conceptional age of 36 to 44 weeks. The duration of individual conventional EEG, the corresponding raw EEG from  $C_3 \rightarrow C_4$ , and the derived aEEG recordings were all equal and ranged from 23 to 145 minutes.

Eighty-one percent of all seizures (691 of 851) originated in the central ( $C_3$  or  $C_4$ ), temporal ( $T_3$  or  $T_4$ ), or midline vertex ( $C_z$ ) electrodes (Table 1). Ninety-four percent (118 of 125) of the conventional EEGs had  $\geq 1$  seizure appearing in the single  $C_3 \rightarrow C_4$  channel. Seventy-eight percent (664 of 851) of the individual seizures were visible in this channel. However, compared with conventional EEG, the seizures in  $C_3 \rightarrow C_4$  were briefer (mean: 132 vs 100 seconds;  $P < .001$ ), less frequent (mean: 7.0 vs 5.2 seizures per hour;  $P < .001$ ), and lower in peak-to-peak amplitude (mean: 145 vs 111  $\mu V$ ;  $P < .001$ ; Table 2). The ratio of ictal to interictal peak-to-peak amplitudes was not significantly different between the conventional and single channel EEG recordings (2.19 vs 2.27; *P* value was not significant).

Using aEEG, the neonatologists detected  $\geq 1$  seizure in a mean of  $40.3\% \pm 16.8\%$  of the 125 records with seizures (range: 21.6%–57.4%) and a mean of  $25.5\% \pm 10.6\%$  of the individual seizures (range: 12%–38%). Only 19 (15%) of 125 aEEG records had  $\geq 1$  seizure detected by all of the neonatologists, and only 1 ( $<1\%$ ) of 125 records had all of the seizures detected by every neonatologist. There were, however, no false-positive seizure detections by any neonatologist among the 19 control records.

On multivariate analysis, factors related to correct seizure detection on aEEG included the neonatologists' experience with aEEG interpretation (comparing the 2 most experienced participants with all of the others combined), as well as seizure duration, frequency, and

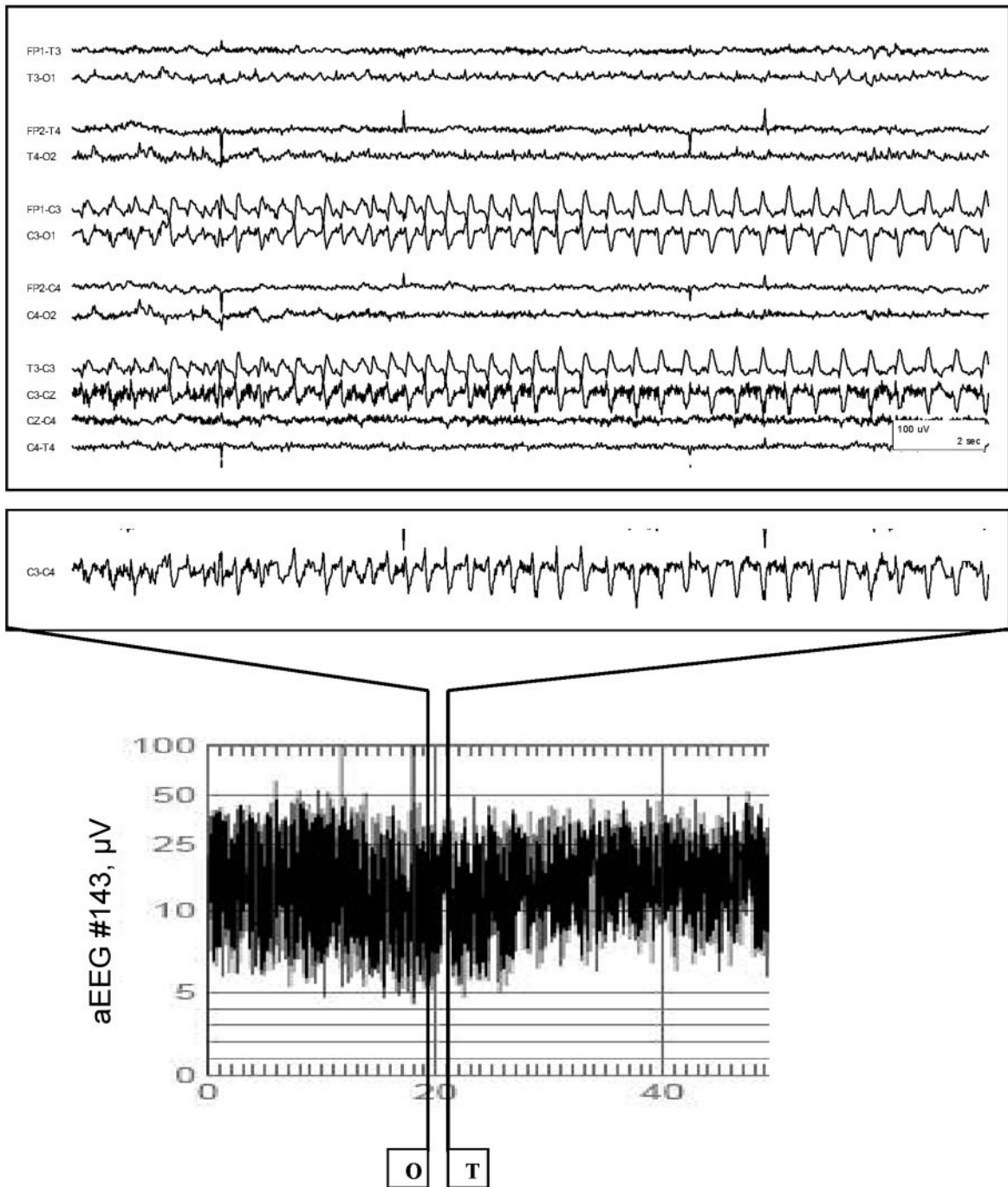


FIGURE 2

Multiple seizures from a 38-week conceptual age infant demonstrated on conventional EEG. Shown is a coincident electrographic seizure in the single C3 → C4 EEG channel and a typical seizure pattern on the corresponding aEEG display. The onset (O) and termination (T) of each aEEG seizure was marked by the neonatologists.

TABLE 1 Distribution of Location of Seizure Onset on Conventional EEG

Location of Seizure Onset	No. (%) of Seizures (n = 851)
Frontal (FP <sub>1</sub> /FP <sub>2</sub> )	39 (5)
Central (C <sub>3</sub> /C <sub>4</sub> /C <sub>2</sub> )	478 (56)
Temporal (T <sub>3</sub> /T <sub>4</sub> )	213 (25)
Occipital (O <sub>1</sub> /O <sub>2</sub> )	121 (14)

amplitude (Table 3). Of note, after adjusting for the interpreter's experience, neither EEG background characterization nor location of seizure onset was significantly associated with seizure detection by aEEG.

#### DISCUSSION

Neonatal seizure is an important and common phenomenon in infants at high risk. The practical difficulties in

**TABLE 2** Quantitative Characteristics of Neonatal Seizures

Characteristics	Conventional EEG	Single Channel EEG (C <sub>3</sub> →C <sub>4</sub> )	<i>P</i> <sup>a</sup>
Seizures detected, <i>N</i> (%)	851	664 (78)	NA
Mean seizure duration, <i>n</i> (range), s	132 (10–2314)	100 (10–2313)	≤.001
Mean No. of seizures per hour, <i>n</i> (range)	7.0 (0.5–21.0)	5.2 (0.0–18.0)	.003
Mean ictal peak-to-peak amplitude, <i>n</i> (range), μV	145 (13–1166)	111 (5–739)	≤.001
Mean ratio of ictal to interictal peak-to-peak amplitudes, <i>n</i> (range)	2.19 (0.50–27.1)	2.27 (0.40–33.8)	.47

NA indicates not applicable.

<sup>a</sup> The *P* value was detected by 2-tailed Student's *t* test.

**TABLE 3** Multivariate Analysis of Factors Related to Correct Detection of Individual Seizures by aEEG

Variable	Odds Ratio	95% Confidence Interval	<i>z</i> Score	<i>P</i>
Seizure visibility in C <sub>3</sub> →C <sub>4</sub>	2.41	1.88–3.08	6.98	<.001
Neonatologists' level of aEEG expertise <sup>a</sup>	2.14	1.87–2.46	10.82	<.001
Seizure count per hour	1.08	1.02–1.13	2.88	.004
Seizure amplitude	1.004	1.003–1.005	6.96	<.001
Seizure duration	1.001	1.001–1.002	7.39	<.001
EEG background <sup>b</sup>				
Mildly abnormal	0.54	0.23–1.24	−1.45	.15
Moderately abnormal	0.93	0.44–1.99	−0.18	.86
Markedly abnormal	1.21	0.56–2.62	0.50	.61
Seizure onset <sup>c</sup>				
Frontal (FP <sub>1</sub> /FP <sub>2</sub> )	1.39	0.93–2.09	1.61	.19
Temporal (T <sub>3</sub> /T <sub>4</sub> )	1.02	0.78–1.38	0.10	.92
Midline (C <sub>z</sub> )	0.96	0.69–1.33	−0.25	.80
Central (C <sub>3</sub> /C <sub>4</sub> )	1.02	0.77–1.37	0.17	.87

<sup>a</sup> The odds ratio for the neonatologists' level of expertise compared the 2 most experienced aEEG interpreters' results with all of the others combined.

<sup>b</sup> The odds ratios for EEG background compared abnormal backgrounds, by category, with records with normal backgrounds.

<sup>c</sup> The odds ratios for seizure locations were calculated relative to occipital onset seizures (O<sub>1</sub>/O<sub>2</sub>).

obtaining expeditious conventional EEG recordings in many NICUs has led to the use of aEEG as an adjunct for electrographic seizure detection. This is the largest published study of the sensitivity of aEEG for neonatal seizure detection. The theoretical ceiling of sensitivity for seizure detection with a single channel of raw EEG (C<sub>3</sub>→C<sub>4</sub>) is high, with 94% of all EEG records with seizures and 78% of all individual seizures detected in the raw EEG channel from which aEEG tracings are derived. However, in this study, the actual sensitivity of electrographic seizure detection by aEEG was low.

Five factors were significantly associated with correct seizure detection by aEEG: the neonatologists' level of expertise in aEEG interpretation, seizure appearance in the raw C<sub>3</sub>→C<sub>4</sub> channel, seizure amplitude, seizure duration, and the number of seizures per hour. The neonatologists with the most aEEG experience identified 38% of all of the individual seizures and 57% of all of the seizure-containing records. However, the other neonatologists, each of whom had ≥1 year of aEEG experi-

ence, detected as few as 12% of individual seizures and 22% of seizure-containing records. Thus, even when interpreted by world experts, many individual electrographic seizures are inherently difficult to detect with aEEG.

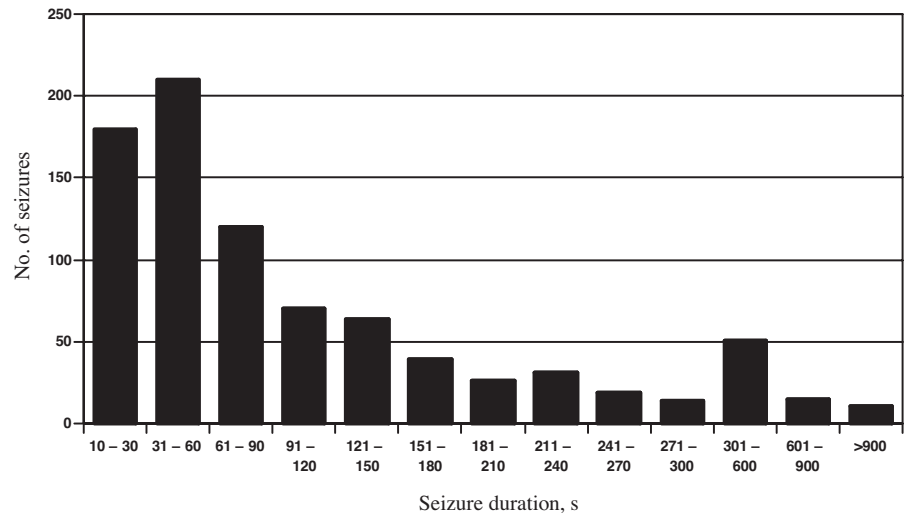
A seizure's appearance in C<sub>3</sub>→C<sub>4</sub> is intuitively related to its visibility on aEEG. It would not be possible to detect a seizure if it was not present in the raw EEG channel from which the aEEG was derived. A large proportion of individual seizures (78%) did appear in the C<sub>3</sub>→C<sub>4</sub> channel, indicating that this location was well-selected. When this factor was included in the multivariate model, other variables describing seizure location (such as seizure onset in the frontal, central, temporal, or occipital electrodes) were not significantly associated with correct seizure detection.

The seizures' peak-to-peak amplitudes were significantly associated with their detection by aEEG. Because aEEG depends heavily on signal amplitude characteristics, detecting a seizure with this type of cerebral function monitor requires the seizure amplitude to be conspicuously higher than the interictal EEG background. The ratio of ictal to interictal peak-to-peak EEG amplitudes in our study was ~2:1. For some seizures, this may prove to be too small to produce consistently discernible ictal deflections on the aEEG, especially if the events are also of brief duration.

Seizure duration was also significantly associated with correct seizure detection. The distribution of seizure duration is heavily weighted to brief events (Fig 3). aEEG is typically displayed at a paper speed of 6 cm/h. The average electrographic seizure detected in the raw C<sub>3</sub>→C<sub>4</sub> channel (100 seconds) corresponds with a deflection of 1.6 mm on an aEEG trace. In isolation, this could be difficult to detect by visual inspection. However, the visual reinforcement of repetitive seizures made it easier to detect individual seizures in aEEG records with high seizure counts per hour, independent of seizure amplitude or duration.

Many conventional electroencephalographers are concerned that repetitive recording artifacts could be misinterpreted as seizures on aEEG. However, none of the neonatologists marked false-positive seizure detections in any of the control records, and there were

**FIGURE 3**  
Distribution of seizure duration. Among the 851 seizures studied, 60% lasted <90 seconds.



remarkably few false-positive seizure notations on the aEEG traces that did have electrographic seizures. This suggests that aEEG has a high specificity for electrographic seizure detection.

In their study of neonatal encephalopathy, al Naqeeb et al<sup>13</sup> described agreement on suspected seizures detected by aEEG among a neonatologist and 2 pediatrics residents ( $\kappa = 0.76$ ) on the aEEGs of 20 of 56 encephalopathic neonates. However, they did not have simultaneous conventional EEG to verify their seizure detections. Another study included 3 patients with electrographic seizures and found that seizures lasting <30 seconds were not detected by aEEG.<sup>20</sup> Our results are consistent with this finding. The 2 most expert neonatologists in our study detected 22% of individual seizures lasting <30 seconds compared with 55% of seizures >30 seconds.

Toet et al<sup>15</sup> reported a study of 33 simultaneously recorded 30-minute conventional EEG and aEEG traces. That study included 10 infants with seizures confirmed on conventional EEG, 8 of whom had  $\geq 1$  seizure detected by simultaneous aEEG. They also noted that low-amplitude seizures and those confined to the occipital or frontal electrodes were often missed on aEEG. In contrast, the current study shows that the location of seizure onset is not significantly associated with seizure detection on aEEG after adjustment for the seizure's appearance in  $C_3 \rightarrow C_4$ . However, we did confirm the finding that low-amplitude seizures were often overlooked on aEEG.

Rennie et al<sup>16</sup> reported on nonexpert use of aEEG for neonatal seizure detection, using a sample of aEEG traces from 19 infants with seizures and 21 without. They found the sensitivity for individual seizure detection to be 38%–55% among their 4 interpreters, higher than our result of 12%–38%. Only 4 of their 19 patients with seizures on aEEG were identified by all of the

neonatologists. The seizures in those records were relatively long (>1 minute) or of unspecified "high amplitude." The authors speculated that the poor sensitivity for neonatal seizure detection by aEEG was largely attributable to their interpreters' lack of experience. However, despite including both internationally recognized experts and less experienced clinicians in our study, we found similarly poor sensitivity. Only 19 of our 125 aEEG records were identified by all of the neonatologists as having seizures, and in only 1 of 125 did all of the interpreters recognize every seizure in the tracing. This implies that there are features inherent both to neonatal seizures and to the aEEG technique that limit the sensitivity of aEEG for neonatal seizure detection.

Several clinical studies of aEEG as a predictor of outcome after neonatal encephalopathy have commented on seizures. However, none had confirmation of the seizures by simultaneous conventional EEG. Toet et al<sup>21</sup> found that the presence of seizures on aEEG at 3 hours of life predicted a poor outcome. However, the absence of seizures was not predictive of good outcome. This result could be partially because of low sensitivity of neonatal seizure detection on aEEG. Hellström-Westas et al<sup>14</sup> found that repetitive seizures correlated with poor outcome after neonatal asphyxia. However, for 6 of these 7 infants, the seizures were clinical and were not detected on aEEG.

Our study had limitations. The EEG records were relatively brief (23–145 minutes) compared with the expanded recording times that are often clinically available with aEEG. It is likely that additional recording time could increase the percentage of records in which  $\geq 1$  seizure is identified, but this would not be expected to increase the proportion of individual seizures detected. Some interpreting neonatologists commented that the records were too brief for them to reach reliable conclusions about the presence of seizures. However, multi-

center studies have used short aEEG traces in their protocols, including the CoolCap Trial,<sup>22</sup> which used a screening 30-minute aEEG as an inclusion criterion. Because short-term aEEG monitoring is used in clinical practice and in research protocols, it was believed that the duration of our recordings was reasonable for the purpose of this study.

The neonatologists who interpreted our aEEG traces did not have access to the raw EEGs. Most modern aEEG equipment allows the interpreter to intermittently call up and display the raw EEG corresponding with a suspicious event observed on the compressed aEEG trace. Therefore, the participating neonatologists were instructed to mark as "seizure" the segments of the aEEG that were suspicious enough to trigger them to look at the raw EEG for confirmation.

The strengths of this study included the use of aEEG traces derived directly from conventional EEG (equivalent to simultaneously recording the 2 techniques), independent interpretation of conventional EEG and aEEG by experts in both methods, and the large sample size, which allowed for analysis of multiple variables of clinical interest (Table 3). As aEEG is introduced into more NICUs, the technique's strengths and shortcomings need to be investigated. Comprehensive studies, such as this contemporary characterization of neonatal seizures on conventional EEG, single-channel EEG, and aEEG, will help to clarify the appropriate role of aEEG in the monitoring and care of neonates with seizures.

## CONCLUSIONS

The clinical detection of seizures by unaided visual inspection of neonates is fraught with hazards of overdiagnosis and underdiagnosis. Although conventional EEG remains the gold standard for neonatal seizure detection and quantification, its limited availability has compelled neonatologists to seek alternative diagnostic methods, such as aEEG. However, there are only limited data from small studies supporting aEEG as a sensitive tool for neonatal seizure detection,<sup>13,15</sup> and some previous data question this assertion.<sup>16</sup> Despite this, inclusion criteria for major studies, such as the CoolCap Trial,<sup>22</sup> have incorporated the presence of seizures on aEEG. We urge neonatologists and neurologists to view aEEG as a useful supplemental tool but not as a replacement for conventional EEG. Although the electrographic background as determined by aEEG has been shown to be predictive of outcome in encephalopathic term neonates,<sup>14,21,23</sup> the aEEG alone has significant limitations in the diagnosis and quantification of neonatal seizures.

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## REFERENCES

1. Eriksson M, Zetterstrom R. Neonatal convulsions: incidence and causes in the Stockholm area. *Acta Paediatr Scand.* 1979;68:807-811
2. Lanska MJ, Lanska DJ, Baumann RJ, Kryscio RJ. A population-based study of neonatal seizures in Fayette County, Kentucky. *Neurology.* 1995;45:724-732
3. Ronen GM, Penney S, Andrews W. The epidemiology of clinical neonatal seizures in Newfoundland: a population-based study. *J Pediatr.* 1999;134:71-75
4. McBride MC, Laroia N, Guillet R. Electrographic seizures in neonates correlate with poor neurodevelopmental outcome. *Neurology.* 2000;55:506-514
5. Scher MS, Painter MJ, Bergman I, Barmada MA, Brunberg J. EEG diagnosis of neonatal seizures: clinical correlations and outcome. *Pediatr Neurol.* 1989;5:17-24
6. Liu X, Muller RU, Huang L-T, et al. Seizure-induced changes in place cell physiology: relationship to spatial memory. *J Neurosci.* 2003;23:11505-11515
7. Liu Z, Yang Y, Silveira DC, et al. Consequences of recurrent seizures during early brain development. *Neuroscience.* 1999;92:1443-1454
8. Rutten A, van Albada M, Silveira DC, et al. Memory impairment following status epilepticus in immature rats: time-course and environmental effects. *Eur J Neurosci.* 2002;16:501-513
9. Clancy RR, Legido ADL. Occult neonatal seizures. *Epilepsia.* 1998;29:256-261
10. Clancy RR, Sharif U, Ichord R, et al. Electrographic neonatal seizures after infant heart surgery. *Epilepsia.* 2005;46:84-90
11. Weiner SP, Painter MJ, Geva D, Guthrie RD, Scher MS. Neonatal seizures: electroclinical dissociation. *Pediatr Neurol.* 1991;7:363-368
12. Hellström-Westas L, Rosen I, de Vries LS, Greisen G. Amplitude-integrated EEG classification and interpretation in preterm and term infants. *Neoreviews.* 2006;7:e72-e87
13. al Naqeeb N, Edwards AD, Cowan FM, Azzopardi D. Assessment of neonatal encephalopathy by amplitude-integrated electroencephalography. *Pediatrics.* 1999;103:1263-1271
14. Hellström-Westas L, Rosen I, Svenningsen NW. Predictive value of early continuous amplitude integrated EEG recordings on outcome after severe birth asphyxia in full term infants. *Arch Dis Child Fetal Neonatal Ed.* 1995;72:F34-F8
15. Toet MC, van der Meij W, de Vries LS, Uiterwaal CS, van Huffelen KC. Comparison between simultaneously recorded amplitude integrated electroencephalogram (cerebral function monitor) and standard electroencephalogram in neonates. *Pediatrics.* 2002;109:772-779
16. Rennie JM, Chorley G, Boylan GB, Pressler R, Nguyen YRH. Non-expert use of the cerebral function monitor for neonatal seizure detection. *Arch Dis Child Fetal Neonatal Ed.* 2004;89:F37-F40
17. Clancy RR, Bergqvist AGC, Dlugos DJ. Neonatal electroencephalography. In: Ebersole J, Pedley T, eds. *Current Practice of*



*Clinical Electroencephalography*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003:160–234

18. Fitzmaurice GM, Laird NM, Ware JH. *Applied Longitudinal Analysis*. Hoboken, NJ: Wiley-Interscience; 2004
19. Hardin WJ, Hilbe MJ. *Generalized Estimating Equations*. Boca Raton, FL: Chapman & Hall/CRC; 2003
20. Murdoch-Eaton DM, Toet M, Livingston J, Smith I, Levene M. Evaluation of the Cerebro Trac 2500 for monitoring of cerebral function in the neonatal intensive care. *Neuropediatrics*. 1994; 25:122–128
21. Toet MC, Hellström-Westas L, Groenendaal F, Eken P, de Vries LS. Amplitude-integrated EEG 3 and 6 hours after birth in full term neonates with hypoxic-ischaemic encephalopathy. *Arch Dis Child Fetal Neonatal Ed*. 1999;81:F19–F23
22. Gluckman PD, Wyatt JS, Azzopardi D, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomized trial. *Lancet*. 2005; 365:663–670
23. Ter Horst HJ, Sommer C, Bergman KA, Fock JM, van Weerden TW, Bos AF. Prognostic significance of amplitude-integrated EEG during the first 72 hours after birth in severely asphyxiated neonates. *Pediatr Res*. 2004;55:1026–1033

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## HOSPITAL CUTS DEADLY INFECTIONS

“At a veterans’ hospital here, nurses swab the nasal passages of every arriving patient to test them for drug-resistant bacteria. Those found positive are housed in isolation rooms behind red painted lines that warn workers not to approach without wearing gowns and gloves. Every room and corridor is equipped with dispensers of foamy hand sanitizer. Blood pressure cuffs are discarded after use, and each room is assigned its own stethoscope to prevent the transfer of micro-organisms. Using these and other relatively inexpensive measures, the hospital has significantly reduced the number of patients who develop deadly drug-resistant infections, long an unaddressed problem in American hospitals. The federal Centers for Disease Control and Prevention projected this year that one of every 22 patients would get an infection while hospitalized—1.7 million cases a year—and that 99 000 would die, often from what began as a routine procedure. The cost of treating the infections amounts to tens of billions of dollars, experts say. But in the past two years, a few hospitals have demonstrated that simple screening and isolation of patients, along with a relentless focus on hygiene, can reduce the number of dangerous infections. By doing so, they have fueled a national debate about whether hospitals are doing all they can to protect patients from infections, which are now linked to more deaths than diabetes or Alzheimer’s disease. At the Veterans Affairs hospital in Pittsburgh, officials say the number of infections with a virulent bacterium known as methicillin-resistant *Staphylococcus aureus*, or MRSA, dropped to 17 cases last year from an average of 60 before the program started. The 40-bed surgical unit that began the experiment in 2001 has cut its infection rate by 78 percent. Such results are not unprecedented. Several European countries, including the Netherlands and Finland, have all but eliminated MRSA through similarly aggressive campaigns. . . . As at other hospitals experimenting with rigorous controls, the Pittsburgh veterans’ hospital has found that preventing infection is cost-effective. Dr Rajiv Jain, the hospital’s chief of staff, said its infection control program cost about \$500 000 a year, including test kits, salaries for three workers and the \$175-per-patient expense of gloves, gowns and hand sanitizer. But the hospital, which has a \$431 million budget, realized a net savings of nearly \$900 000 when the number of infected patients fell. . . . Eighteen states now require hospitals to publish their infection rates. Last month, legislatures in New Jersey and Illinois approved bills that would make those states the first to require hospitals to screen all intensive-care patients for MRSA.”

Sack K. *New York Times*. July 27, 2007

Noted by JFL, MD

# Sensitivity of Amplitude-Integrated Electroencephalography for Neonatal Seizure Detection

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