Seizure identification in the ICU using quantitative EEG displays

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ABSTRACT

Objective: To evaluate the diagnostic accuracy of 2 quantitative EEG display tools, color density spectral array (CDSA) and amplitude-integrated EEG (aEEG), for seizure identification in the intensive care unit (ICU).

Methods: A set of 27 continuous EEG recordings performed in pediatric ICU patients was transformed into 8-channel CDSA and aEEG displays. Three neurophysiologists underwent 2 hours of training to identify seizures using these techniques. They were then individually presented with a series of CDSA and aEEG displays, blinded to the raw EEG, and asked to mark any events suspected to be seizures. Their performance was compared to seizures identified on the underlying conventional EEG.

Results: The 27 EEG recordings contained 553 discrete seizures over 487 hours. The median sensitivity for seizure identification across all recordings was 83.3% using CDSA and 81.5% using aEEG. However, among individual recordings, the sensitivity ranged from 0% to 100%. Factors reducing the sensitivity included low-amplitude, short, and focal seizures. False-positive rates were generally very low, with misidentified seizures occurring once every 17–20 hours.

Conclusions: Both CDSA and aEEG demonstrate acceptable sensitivity and false-positive rates for seizure identification among critically ill children. Accuracy of these tools would likely improve during clinical use, when findings can be correlated in real-time with the underlying raw EEG. In the hands of neurophysiologists, CDSA and aEEG displays represent useful screening tools for seizures during continuous EEG monitoring in the ICU. The suitability of these tools for bedside use by ICU nurses and physicians requires further study. *Neurology*® 2010;75:1501–1508

GLOSSARY

aEEG = amplitude-integrated EEG; **CDSA** = color density spectral array; **FFT** = fast-Fourier transformation; **ICU** = intensive care unit.

Nonconvulsive seizures occur in 16%–48% of selected critically ill patients, and may contribute to brain injury if untreated.^{1–12} Detection of nonconvulsive seizures requires continuous EEG. Increasing awareness about nonconvulsive seizures has led to a growing demand for continuous EEG monitoring in ICUs. To facilitate interpretation of prolonged EEG recordings, several quantitative EEG display tools have been developed to highlight significant electrographic events and provide insight into EEG trends over time.

Amplitude-integrated EEG (aEEG) depicts time-compressed and rectified EEG amplitude on a semi-logarithmic scale, and is now commonly employed to monitor cerebral function in neonates.¹³ While aEEG provides an accurate measure of neonatal EEG background,^{14,15} its utility for seizure identification remains a matter of debate.^{16–18} To date, reports on the use of aEEG for seizure identification in pediatric and adult ICUs have been few and descriptive.^{19–22}

Color density spectral array (CDSA) applies fast-Fourier transformation (FFT) to convert raw EEG into a time-compressed and color-coded display, also termed a color spectro-

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gram.^{23–25} Clinical applications of CDSA and related techniques have included monitoring depth of sedation,²⁶ detecting cerebral ischemia,²⁷ and identifying seizures in adults, children, and neonates.^{28–30}

While past reports indicate that CSDA and aEEG show promise for the detection of seizures in the ICU, a formal assessment of their diagnostic accuracy is lacking. Therefore, our objective was to critically evaluate the sensitivity and false-positive rates of both CSDA and aEEG for seizure identification in a pediatric ICU.

METHODS **Standard protocol approvals, registrations, and patient consents.** Our hospital's Research Ethics Board approved this study and granted a waiver of informed consent. Using a clinical database, we identified continuous EEG recordings performed in patients aged 31 days to 18 years in our pediatric ICU between June 2003 and May 2008. We included continuous EEG recordings of at least 8 hours' duration that were performed for the following indications: refractory status epilepticus; suspicion of nonconvulsive seizures in a patient deemed to be at risk; suspicion of seizures in a patient managed with neuromuscular blocking agents; or to characterize clinical events suspected to represent seizures. We excluded EEG recordings containing more than 100 seizures per 8-hour epoch because these would have been impractical to evaluate using the study methodology detailed below.

EEG recordings and interpretation. Digital EEG recordings employed either a reduced neonatal montage (11 electrodes) or a full montage (19 electrodes) applied according to the international 10–20 system, plus a reference electrode located at Pz'.

Recordings were sampled at 200–500 Hz using a 32-channel Lamont amplifier with hardware filters at 0.1 and 70 Hz. All recordings were de-identified and then reviewed by a board-certified electroencephalographer (C.H.), who was not aware of any clinical data. Electrographic seizures were identified using published criteria.³¹ In all ambiguous cases, a second board-certified electroencephalographer (A.O.) was consulted, and a consensus was reached. Recordings containing waxing and waning electrographic activity on the interictal–ictal continuum were included in the study,³¹ but only ictal electrographic events with a clear onset, evolution in frequency, amplitude, or morphology, and clear offset were classified as seizures. Consecutive seizures were classified as distinct events when they were separated by more than 20 seconds of interictal EEG; otherwise they were classified as 1 continuous seizure.

CDSA and aEEG transformations. Continuous EEG recordings were subjected to CDSA and aEEG transformation using the quantitative EEG tools built into the Harmonie EEG reviewing software (Stellate Systems Inc., Montreal, Canada). Transformations were performed on an 8-channel, double distance longitudinal bipolar montage (Fp1-C3, C3-O1, Fp1-T3, T3-O1; Fp2-C4, C4-O2, Fp2-T4, T4-O2). CDSA transformation employed a FFT for frequencies between 0 and 20 Hz, using FFT epochs of 2.56 seconds averaged over a 20-second cosine tapering window with no overlap. The frequency-specific power from 0 to 20 Hz was visually represented using a color scale, with black representing low power, and orange, yellow, and white representing successively higher power. aEEG was displayed on a conventional semi-logarithmic scale (linear from 0 to 10 μ V and logarithmic from 10 to 200 μ V). Eight hours of CDSA and aEEG data were displayed per screen on a 24-inch high-resolution (1,600 $\times$ 1,200 pixels) display, such that a single horizontal pixel represented exactly 20 seconds of raw EEG data.

Evaluation of CDSA and aEEG tools. Three neurophysiologists participated in this study. All were board-certified, with

Figure 1 EEG recordings studied and overall performance using CDSA and aEEG displays

Ability of reviewers to discriminate between the presence or absence of seizures in a given EEG recording using color density spectral array (CDSA) and amplitude-integrated EEG (aEEG) (based on median values).

Figure 2 Color density spectral array (CDSA) and amplitude-integrated EEG (aEEG) testing displays

With the raw EEG tracing concealed, neurophysiologists were individually presented with either an 8-channel CDSA display (A) or an 8-channel aEEG display (B). Participants were instructed to “mark any epochs that they suspected to be seizures.” Their performance was compared to seizures identified by analysis of the raw EEG, as indicated in the top channel (concealed during testing).

at least 5 years of conventional EEG reading experience, but none had any prior experience using CDSA or aEEG. Participants first underwent 2 hours of training, during which they were introduced to the theoretical basis of CDSA and aEEG, followed by extensive hands-on training on the recognition of seizures and various artifacts, employing a training set of 7 continuous EEG recordings performed in the pediatric ICU. During training, participants had the opportunity to view CDSA or aEEG displays simultaneously with the underlying raw EEG, permitting them to learn the appearance of seizures, interictal waveforms, and various artifacts. Following training, partici-

pants were then individually evaluated on their ability to identify seizures using the CDSA display or aEEG display employing a testing set of 27 continuous EEG recordings: 17 containing seizures and 10 control files without seizures (figure 1). There was no overlap between the training and testing sets of recordings. During testing, participants were presented with either a CDSA display or an aEEG display (figure 2), without access to the corresponding raw EEG. Participants received scripted instructions to mark any epochs that they suspected to be seizures. Marking was accomplished using the digital review software by using a single-pixel cursor to place an annotation marker for each sus-

pected seizure. Participants had no knowledge of the presence or absence of seizures in a given recording, or any other clinical information. Participants were permitted to scroll forwards and backwards as desired through multiple 8-hour screens of data, and there was no time limit imposed. Participants were supervised during all testing, and each was presented with EEG recordings in a different random order.

Analysis. The sensitivity for seizure identification and the false-positive rate per hour were calculated by comparing the suspected seizures that had been marked by the neurophysiologists on CDSA and aEEG displays to the seizures identified by the gold standard analysis of the raw EEG. Correct identifications were credited when a mark was placed on a seizure, or within 30 seconds of the seizure onset or offset. False-positives were defined as a mark placed anywhere else in the recording. Fleiss κ for multiple raters was calculated to determine the level of interrater agreement above chance. Statistical analyses were performed using SPSS 15.0 (SPSS Inc., Chicago, IL) and SAS v 9.1.2 (SAS Institute Inc., Cary, NC).

RESULTS Table 1 summarizes the characteristics of the 27 continuous EEG recordings comprising the testing set: 17 recordings containing seizures and 10 control recordings without seizures. The recordings comprised 487 hours of EEG containing a total of 553 seizures. The most common indications for continuous EEG monitoring were refractory status epilepticus and the suspicion of nonconvulsive seizures. Diagnoses among patients undergoing EEG monitoring were varied, the most common being hypoxic-ischemic encephalopathy, meningitis/encephalitis, epilepsy, and genetic/metabolic disease (see table e-1 on the *Neurology*[®] Web site at www.neurology.org for details). Figure 1 illustrates the accuracy of CDSA and aEEG for discriminating between the presence or absence of seizures in a given EEG recording.

Sensitivity. Table 2 presents the sensitivities for seizure identification using CDSA and aEEG compared to the gold standard interpretation of the underlying raw EEG. When considering sensitivity across all EEG recordings, the 3 neurophysiologists correctly identified a median of 83.3% (range 73.3%–86.7%) of seizures per recording using CDSA and a median of 81.5% (range 80.6%–83.9%) of seizures per recording using aEEG. However, when considering sensitivity on individual EEG recordings, performance was considerably more variable, as illustrated in figure 3. The median seizure identification rate was 75% or greater among 10 recordings (59%) using CDSA and 11 recordings (65%) using aEEG. The median seizure identification rate was 50% or greater among 14 recordings (82%) using CDSA and 15 recordings (88%) using aEEG. The median seizure identification rate was 25% or less among 3 recordings (18%) using CDSA and 1 recording (6%)

Table 1 Characteristics of continuous EEG recordings and patients

Characteristics	Values
Total no. of EEG recordings	27
Indication for EEG, n	
Refractory status epilepticus	17
Suspicion of nonconvulsive seizures	8
Characterization of clinical events suspected to be seizures	1
Suspicion of seizures in patient receiving neuromuscular blocking agents	1
Duration of recording, h, mean (range)	18.0 (10–24)
Initial EEG background, n	
Slowing (generalized or focal)	20
Burst suppression	3
Attenuation	3
Alpha coma	1
No. of recordings containing seizures	17
Total no. of seizures	553
Seizure count per recording, mean (range)	32.5 (6–68)
Seizure count per hour of recording, mean (range)	1.8 (0.3–3.9)
Seizure duration, s, mean (range)	214 (20–2,760)
Seizure distribution, %	
Bilateral	67
Hemispheric	20
Focal	13
Total no. of patients studied	22
Age, mean (range)	4.2 y (1.5 mo–12.3 y)
Primary diagnosis, n	
Hypoxic-ischemic encephalopathy	5
Meningitis/encephalitis	4
Epilepsy	4
Genetic/metabolic disease	4
Inflammatory brain disease	2
Brain tumor	2
Sepsis	1

using aEEG. Each of the 3 reviewers encountered at least 1 recording in which they missed all seizures on CDSA, aEEG, or on both displays.

Missed seizures. Overall, 10.5% of seizures were completely missed by all 3 reviewers on both CDSA and aEEG displays. Significantly more seizures were completely missed when using CDSA (21.2%) than when using aEEG (14.31%) ($p = 0.003$, χ^2). Among individual EEG recordings, seizures were

Table 2 Sensitivity and false-positive rate for seizure identification using CDSA and aEEG^a

	CDSA		aEEG	
	Sensitivity, %	False-positive rate, n/h	Sensitivity, %	False-positive rate, n/h
Median of 3 neurophysiologists	83.3	0.06	81.5	0.05
Reviewer 1	73.3 (0-100)	0.06 (0-4.08)	80.6 (0-100)	0.05 (0-0.45)
Reviewer 2	86.7 (0-100)	0.00 (0-1.39)	81.5 (6.25-100)	0.19 (0-1.47)
Reviewer 3	83.3 (0-100)	0.13 (0-7.66)	83.9 (0-100)	0.00 (0-0.65)

Abbreviations: aEEG = amplitude-integrated EEG; CDSA = color density spectral array.

^a Values for individual reviewers are median (range) across all EEG recordings.

completely missed by at least 1 reviewer in 4 recordings (see table e-2). For example, in recordings 16 and 17, every reviewer missed every seizure using CDSA, whereas 2 or more reviewers were able to identify at least some of the seizures using aEEG. Similarly, in recording 15, the sensitivity for seizure identification using aEEG was much higher than using CDSA. Individual variability in interpretation was apparent in recording no. 3: whereas 2 of the reviewers identified every seizure, the third reviewer missed every seizure on both CDSA and aEEG, possibly because they were misinterpreted as an artifact. Missed seizures generally fell into one of the following categories: seizures of low voltage ($<75 \mu\text{V}$), seizures of short duration (<1 min), seizures that remained focal, or seizures that occurred in the con-

text of abundant interictal epileptiform discharges (see figure e-1 for examples).

False-positive rate. Table 2 presents the median rates of false-positive seizure identification by neurophysiologists across all EEG recordings. Overall, these false-positive rates were quite low, corresponding to 1 false-positive per 17 hours of CDSA, and 1 false-positive per 20 hours of aEEG displayed. False-positive rates were similar among the 17 files containing seizures and 10 control files without seizures. However, false-positive rates did vary among the 27 individual recordings (figure 3). Two EEG recordings (nos. 18 and 11) resulted in particularly high median false-positive rates when interpreted using CDSA. Recording 18 contained a burst-

Figure 3 Sensitivity and false-positive rates of color density spectral array (CDSA) and amplitude-integrated EEG (aEEG) for seizure identification among individual EEG recordings

Bars represent median values for all 3 neurophysiologists, with error bars indicating the range of values obtained by individual reviewers.

suppression pattern, which was misidentified as seizures by 1 reviewer. Recording 11 contained periodic epileptiform discharges, which were misidentified as seizures by 2 reviewers. False-positives in the remainder of recordings were far less frequent, and fell into 1 of 3 categories: non-ictal electrographic events, movement or electrode artifact, and no clear change on EEG (see figure e-2 for examples).

Interrater agreement. κ scores, a measure of interrater agreement above that expected by chance alone, indicated substantial agreement among all neurophysiologists when using CDSA ($\kappa = 0.78 \pm 0.06$) and moderate agreement ($\kappa = 0.54 \pm 0.06$) when using aEEG to identify seizures.³²

DISCUSSION This study provides novel evidence to support the clinical utility of CDSA and aEEG for seizure identification in the ICU. Following 2 hours of training, neurophysiologists without prior experience using CDSA or aEEG were able to use these techniques to identify 81%–83% of seizures. False-positive rates for both techniques were very low, with misidentified seizures occurring every 17–20 hours. Interrater agreement was substantial using CDSA and moderate using aEEG.³²

The closest point of comparison for our work is a series of studies conducted in neonates. Using a similar quantitative EEG technique known as envelope trend, experienced users of a 6-channel envelope trend display demonstrated a sensitivity of 88% for identifying long discrete seizures, 40% for brief seizures, and 20% for slowly evolving seizures, with false-positive rates of 0–2 per hour.²⁸ Several other studies in neonates have evaluated 1- or 2-channel aEEG displays, reporting a wide range of sensitivities for seizure identification from 26% to 76%.^{16–18,33} This variability in results can be attributed to differences in study methods, including the level of experience of the aEEG reviewers, the length of recordings, paper speed, number of aEEG channels, and whether or not reviewers had access to the underlying raw EEG tracing. Nevertheless, based in part on evidence from these reports, 1- and 2-channel aEEG displays are now commonly employed for seizure identification in many neonatal ICUs.

The sensitivity of the CDSA and aEEG techniques employed in the present study is higher than in these previous reports, despite the fact that our participants had no prior experience with these techniques, and did not have access to the underlying raw EEG during their analysis. We hypothesize that the higher sensitivity observed in our study may be because our CDSA and aEEG displays included more channels (8 channels vs 6, 2, or 1), or perhaps be-

cause CDSA and aEEG may be more effective at depicting seizures in children than in neonates.

Overall, approximately 20% of seizures were missed using both CDSA and aEEG displays. Among EEG recordings in which more than half of seizures were missed, the only common characteristic of missed seizures was low amplitude ($<75 \mu\text{V}$). Both CDSA and aEEG displays are at least partially amplitude-based. Insensitivity to low-amplitude seizures has been noted in several studies of aEEG among neonates,^{18,33,34} and other FFT-based displays in adults (i.e., total power).⁴ Interestingly, the performance of aEEG at detecting these low-amplitude seizures was superior to CDSA, suggesting that aEEG may be more sensitive to seizures of low amplitude. Other characteristics of missed seizures included short duration (<1 minute) and seizures that remained focal. Difficulty detecting short seizures is a known limitation of aEEG, due to time compression of the display.³³ The degree of time compression required to display 8 hours of data on our high-resolution 24-inch display was similar to that of commercial aEEG machines displaying 3 hours of data on a smaller screen. Difficulty detecting focal seizures on aEEG has also been reported.³³ Our 8-channel montage was designed to mitigate this effect, but the most poorly scored recording (no. 17) contained only focal seizures; however, these seizures were also of extremely low amplitude ($40\text{--}60 \mu\text{V}$), which could also account for their poor detectability. The clinical significance of the low-amplitude, short or focal seizures that were missed is uncertain. Finally, identifying seizures that occurred in the context of abundant interictal epileptiform discharges or high-amplitude, generalized background slowing also proved difficult in some cases, a limitation that has been noted previously.¹⁹

False-positives for all reviewers across all recordings were marked at a very low rate, occurring once every 17–20 hours of recording. False-positives were sometimes associated with movement or electrode artifact, a noted limitation of quantitative EEG displays.^{19,25} Two particular recordings demonstrated much higher false-positive rates on CDSA due to misinterpretation of either a burst-suppression pattern or periodic epileptiform discharges. Had our participants been given access to the underlying raw EEG tracing, the nonictal nature of these patterns would have been easily confirmed, further reducing the false-positive rate.

This study has limitations. By necessity, our study design concealed the underlying raw EEG in order to measure the performance of neurophysiologists based solely on their interpretation of the CDSA or aEEG displays. In real-world clinical use, CDSA and

aEEG should be used as screening tools to identify timepoints of interest during a prolonged EEG recording that warrant closer inspection using the raw EEG. Clinical users of CDSA and aEEG would be able to confirm their findings on the raw EEG, and have the opportunity to learn particular patterns indicative of seizures or artifacts that may be unique to individual patients, resulting in improved accuracy. Without access to the raw EEG, our reviewers were at a disadvantage. Therefore, our results likely represent conservative estimates of the accuracy of CDSA and aEEG. In clinical use, we would anticipate fewer false-positives and possibly greater sensitivity for seizure identification. Greater experience in the use of these techniques may further improve their accuracy. Although we strove to study a representative sample of continuous EEG recordings from our pediatric ICU, our findings may not be generalizable to other pediatric or adult centers because of potential differences in patient populations. Furthermore, the accuracy of CDSA and aEEG may vary with different EEG recording techniques (i.e., number of channels, amount of EEG data displayed per screen) or with different patient populations (i.e., adults or neonates). Future studies could provide insight on the merits of using different time scales (i.e., 2–4 hours per screen), averaged data from multiple EEG channels, or other quantitative EEG modalities either alone or in combination, such as total power, α/δ ratio, an asymmetry index, or a rhythmicity index.

Our findings demonstrate that CDSA and aEEG displays are useful screening tools for seizures in the ICU when used by trained neurophysiologists who are aware of the techniques' inherent limitations. However, these displays do not replace careful review of conventional EEG data. Given the widespread incorporation of these display tools into current EEG software by many vendors and the limited training required for their use, these techniques appear amenable to widespread adoption. Whether these displays are suitable for bedside use by ICU nurses and physicians without prior training in electroencephalography requires further study.

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