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ORIGINAL ARTICLE

Rapid Bedside Evaluation of Seizures in the ICU by Listening to the Sound of Brainwaves: A Prospective Observational Clinical Trial of Ceribell's Brain Stethoscope Function

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Abstract

Background: Patients suffering from non-convulsive seizures experience delays in diagnosis and treatment due to limitations in acquiring and interpreting electroencephalography (EEG) data. The Ceribell EEG System offers rapid EEG acquisition and conversion of EEG signals to sound (sonification) using a proprietary algorithm. This study was designed to test the performance of this EEG system in an intensive care unit (ICU) setting and measure its impact on clinician treatment decision.

Methods: Encephalopathic ICU patients at Stanford University Hospital were enrolled if clinical suspicion for seizures warranted EEG monitoring. Treating physicians rated suspicion for seizure and decided if the patient needed antiepileptic drug (AED) treatment at the time of bedside evaluation. After listening to 30 s of EEG from each hemisphere in each patient, they reevaluated their suspicion for seizure and decision for additional treatment. The EEG waveforms recorded with Ceribell EEG were subsequently analyzed by three blinded epileptologists to assess the presence or absence of seizures within and outside the sonification window. Study outcomes were EEG set up time, ease of use of the device, change in clinician seizure suspicion, and change in decision to treat with AED before and after sonification.

Results: Thirty-five cases of EEG sonification were performed. Mean EEG setup time was 6 ± 3 min, and time to obtain sonified EEG was significantly faster than conventional EEG ($p < 0.001$). One patient had non-convulsive seizure during sonification and another had rhythmic activity that was followed by seizure shortly after sonification. Change in treatment decision after sonification occurred in approximately 40% of patients and resulted in a significant net reduction in unnecessary additional treatments ($p = 0.01$). Ceribell EEG System was consistently rated easy to use.

Conclusion: The Ceribell EEG System enabled rapid acquisition of EEG in patients at risk for non-convulsive seizures and aided clinicians in their evaluation of encephalopathic ICU patients. The ease of use and speed of EEG acquisition and interpretation by EEG-untrained individuals has the potential to improve emergent clinical decision making by quickly detecting non-convulsive seizures in the ICU.

Keywords: Electroencephalography, Sonification, Status epilepticus, Clinical trial

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Introduction

Most seizures in the critical care unit are subclinical and have a significant impact on morbidity, mortality and neuronal health [1–8]. These seizures are only detectable through electroencephalography (EEG) monitoring. EEG is not universally available, however, and many hospitals do not have EEG platforms with appropriate staff to set up and interpret results [9]. Where EEG is not readily available, patients suspected of having subclinical seizures must be transferred to obtain EEG monitoring, delaying diagnosis and treatment. When EEG is available, there may be significant delays in obtaining EEG data due to the limited availability of EEG technicians and neurologists. Even in modern academic medical centers, it takes hours from the EEG order to first EEG recording [9, 10], with the final formal interpretation of the EEG by attending physicians taking even longer. Delayed diagnosis and treatment of non-convulsive seizures or status epilepticus leads to higher morbidity, mortality and length of hospital stay [11, 12].

The Ceribell EEG System (Ceribell Inc., Mountain View, CA) was developed to address the current limitations in EEG acquisition and interpretation. The device recently received approval from the US Food and Drug Administration, and consists of a handheld recording device linked to a single-use 10 lead EEG headband which is placed around the patient's head (over the hair) by the treating clinician (Fig. 1). Soft plastic prongs on the inside of the headband connect to the scalp through the hair, and dispense electrode gel under each lead to optimize the EEG signal. The device displays the recorded EEG data on its screen and transmits the EEG data wirelessly to a cloud destination for visual review by trained neurologists. At the same time, its *Brain Stethoscope* function converts the EEG signal to sound using a proprietary sonification algorithm running in real time with no distortion of temporal information. Normal EEG patterns are heard as monotone sounds, while abnormal EEG fluctuations caused by seizure discharges are heard as repetitive sharp fluctuations in tone. A recent study assessing the validity of Ceribell sonification by individuals untrained in EEG interpretation showed that medical students and nurses could detect ongoing seizures with ~ 98 and 95% sensitivity compared to neurology experts reviewing the same EEGs on visual display [13].

The goal of EEG sonification is to allow swift interpretation of the EEG by medical professionals at the bedside who are not trained in EEG analysis. The sonification of EEG is not meant to replace the formal review of visual EEG by trained neurologists as the sonification of Ceribell EEG data applies only to one single temporal channel of EEG on each hemisphere. Therefore, the overarching goal of the current study was not to measure the diagnostic value of the Ceribell EEG system in its entirety but only the clinical value of its *Brain Stethoscope* function. The assessment of one channel EEG by sound is inherently designed to capture hemispheric and or bilaterally generalized events such as non-convulsive status epilepticus and cannot and should not replace a formal retrospective review of the EEG waveforms within a longer period of recording.

Our current study aimed to assess the accuracy of the sonified EEG in confirming (true positive) or ruling out (true negative) non-convulsive hemispheric or generalized seizures in an intensive care unit (ICU) setting. We also sought to assess whether sonification would change clinician suspicion for seizure and likelihood to treat with antiepileptic drugs (AEDs) and compare the user satisfaction rating and the time to obtain Ceribell handheld EEG to the time to obtain conventional EEG.

Methods

Patients

This was a prospective cohort study of patients admitted to the ICUs at Stanford University Hospital between January and June 2016. Patients were included in the study if they were admitted to an ICU and had altered mental status, defined as a Glasgow Coma Scale (GCS) < 12, and in whom continuous EEG monitoring was planned to rule out non-convulsive seizures as the cause of encephalopathy. Patients were only recruited if informed consent

Fig. 1 The Ceribell EEG system. The Ceribell EEG System consists of a handheld recording device connected to a 10-lead 8-channel EEG headband. The recording device displays and records the EEG waveform and converts the EEG to sound through a sonification algorithm

could be obtained from patients' families. Patients were excluded if they were < 18 years of age, were pregnant, or were uncooperative or combative to the point that EEG could not be placed. Demographic information, including age, sex, primary diagnosis, GCS, intubation status, and time from admission to EEG monitoring was recorded for each patient. Patient were enrolled between 7:00 AM and 5:00 PM due to limited research coordinator coverage overnight. The study was approved by the Stanford University Institutional Review Board. Informed consent was obtained from each patient's surrogate decision maker (patients were unable to consent for themselves due to GCS < 12).

Study Personnel

All handheld EEG sonifications were performed by attending neurointensivists ($N = 2$) or neurology fellows ($N = 5$) rotating on the neurocritical care service. Prior to beginning the study, a brief (~ 4 min) training video on interpretation of sonified EEG was viewed by all study personnel (video URL: https://youtu.be/JWKpzCsEESk). The video was also available for review as needed throughout the study. In the training video, participants were instructed that seizures are loud, rhythmic fluctuations in sound, unlike singular and isolated discharges that would occur in slow or normal EEGs. Periodic and repetitive rhythmic discharges such as lateralized generalized periodic discharges would sound like seizure if they were occurring frequently. In addition, movement of the patient or device could cause fluctuation in sound. For this reason the device was laid next to the patient on the bed during sonification, and care was taken to ensure the patient was not moving during sonification. Study personnel were trained on placement of the handheld EEG headband and use of the system. The set up training video can be viewed at the following URL: https://youtu.be/dENIUQd_elU

Study Device

The Ceribell EEG system (Fig. 1) is a device consisting of a 10 lead headband connected to a handheld device that sonifies EEG signal, records and displays visual EEG waveforms and transmits them wirelessly in real time to a remote reading station. The device is placed around the head with leads 5 and 10 nearest the occiput and the headband fastening in the front over the forehead. Odd-numbered leads are on the left and even-numbered leads on the right. For this study, the visual waveform analysis was not utilized (clinicians were unable to see the waveform display); suspicion for seizure and likelihood to treat were based solely on the sonified EEG signal. The Ceribell recording device records EEG in bipolar montage at a sampling rate of 250 cps, and no digital manipulation is applied to the raw EEG signal before sonification. The raw EEG signal modulates a career voice signal in real-time speed without any time compression (i.e., speeding up the playback). Sonification is applied to one channel of EEG (one temporal channel on each side). Because the device has 10 electrodes, only 8 channels of visual EEG are displayed, similar to the lateral channels of the double banana montage.

Study Procedure

The study procedure is illustrated in Fig. 2. Upon identification of a study candidate, research coordinators were immediately notified and obtained rapid in-person or telephone consent from the patient's surrogate decision maker. Conventional EEG was ordered per standard-of-care and was not delayed due to participation in the study. The treating physician placed the handheld EEG on the patient and confirmed adequate connection from all leads. Prior to sonification, the participating physician reviewed the patient's medical history and comorbidities, and performed an independent neurologic examination. They then completed a questionnaire (Pre-sonification rating) asking them to rate (1) their degree of suspicion for seizure (5-point scale; 1 = low suspicion, 5 = high) and (2) their intention to treat with an anti-epileptic medication (Treat/Not Treat/Not Sure). Sonification was then performed for 30 s per hemisphere (1 min total). After sonification was complete, the same two questions were answered (Post-sonification rating). The physician also answered questions about ease of use of the headband and recording device (5-point scale; 1 = challenging, 5 = easy).

After the participating physician answered the study questions, the handheld EEG continued to record until the EEG technicians arrived at the bedside to connect the patient to the hospital's conventional EEG system (Nihon Kohden, Tokyo, Japan). Sonification was not continued beyond the 1-min initial assessment. The headband was removed and the handheld EEG recording stopped at the time of conventional EEG placement. The headband was removed prior to placement of conventional EEG if the patient needed emergent imaging or other procedures. The recorded Ceribell handheld EEG visual waveforms were later analyzed by two blinded epileptologists (each with > 15 years of experience interpreting EEG) to determine if seizures occurred during the sonification period or at any time throughout the entire recording. A third blinded reviewer was used in cases of disagreement between the two. The interpretation of the handheld visual EEG data was then compared to the investigators' bedside interpretation of the sonified EEG. Each patient's conventional hospital EEG report was later analyzed to determine whether or not seizures occurred over the

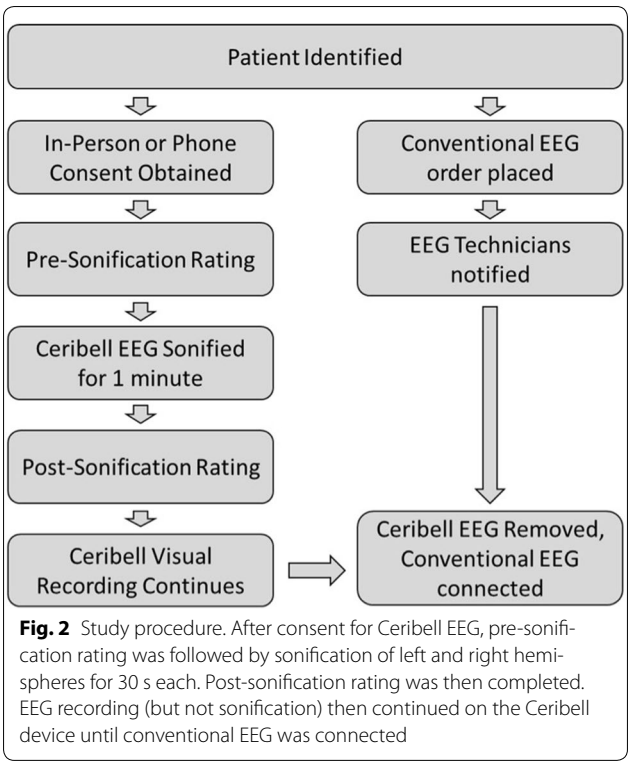

Fig. 2 Study procedure. After consent for Ceribell EEG, pre-sonification rating was followed by sonification of left and right hemispheres for 30 s each. Post-sonification rating was then completed. EEG recording (but not sonification) then continued on the Ceribell device until conventional EEG was connected

next day of monitoring, and the results of the handheld system's sonified EEG and visual EEG was correlated with the conventional EEG results. We used the International League Against Epilepsy definition of non-convulsive status epilepticus, i.e., prolonged seizure activity without motor symptoms lasting more than 10 min.

The study endpoints included: (1) time required to connect the handheld EEG system, (2) time from placement of the EEG order to start of handheld EEG system versus start of conventional EEG recording, (3) ease of use of the handheld EEG system and accompanying headband, (4) change in degree of suspicion for seizure after sonification, (5) change in physician's decision to treat with antiepileptic medications after EEG sonification, and (6) accuracy of change in treatment decision.

Statistical Analysis

For each of the EEGs, we determined the *accuracy* of the participating physician's rating of sonified EEG based on the presence or absence of seizures determined by the two blinded epileptologists reviewing the same EEG epochs on visual display. Sensitivity and specificity to identify non-convulsive seizures was assessed by dichotomizing suspicion at 1–3 (no seizure) versus 4–5 (seizure) scores and using blinded waveform analysis as the gold standard. Because there was a "Not Sure" category for treatment decision, two analyses were done, classifying the "Not Sure" cases as "Treat" and another grouping them with "Not Treat." Changes in suspicion and treatment decision were then assessed using a McNemar test, stratified by true seizure status. Differences in times to recording between the Ceribell EEG and conventional EEG were compared using the Wilcoxon signed ranks test. All reported confidence intervals are at the 95% level.

Results

Demographic information and patient clinical characteristics are described in Table 1. In total, 35 sonifications were carried out on 34 individual patients (one patient was sonified twice for separate episodes of encephalopathy ~ 2 weeks apart). Mean patient age was 61 (SD 18) years, and 34% were female. Median Glasgow Coma Scale (GCS) was 6 (IQR 4–8.5), and median time from admission to EEG was 6 days (IQR 2–18). Eighty-three percent of patients were intubated, and 40% of patients had a primary neurologic diagnosis on admission.

Mean set up time for the Ceribell EEG was 6 ± 3 min. Median time from EEG order to Ceribell EEG was 23 min (IQR 14–46) versus 145 min (IQR 93–237) for conventional EEG ($p < 0.001$), with a median difference of 86 min (IQR 60–152). Mean recording time with the Ceribell EEG system was 55 ± 37 min. Six patients had a procedure in between Ceribell EEG recording and conventional EEG set up (1 patient went to emergently to the operating room, 1 patient underwent cardiac catheterization, 1 patient had EVD placed, 3 patients had CT head). On a scale of 1 (very difficult) to 5 (very easy), participating physicians rated the ease of use of the Ceribell headband and the Ceribell EEG recording device as 4.51 ± 0.85 and 4.97 ± 0.17, respectively.

Considering all 35 cases, treatment decision changed in 14 cases (40%). In the following text, we will describe these changes for True Positive and True Negative cases separately. The gold standard is defined by retrospective review of Ceribell visual EEGs by three EEG trained epileptologists.

Handheld EEG captured one case of non-convulsive status epilepticus (NCSE). This subject had a large ischemic stroke and was unresponsive with GCS 3. A sample of the patient's visual EEG is presented in Fig. 3 and sound samples from the left and right hemispheres in this subject are presented in Supplementary Video #1. The subject had abnormal sonification resulting in a suspicion for seizure change from 1 before sonification to 5 afterward, and treatment decision changed from "Not Treat" to "Treat." An additional patient was identified as having seizure due to frequent abnormal discharges heard on sonification; he was judged as having left hemispheric "seizure-like" rhythmic periodic waveforms on blinded EEG review during

Table 1 Demographics and clinical characteristics

Number of patients	34[a]
Age, mean ± SD, (range)	61 ± 18 (22–89)
Female, *n* (%)	12 (35%)
Median GCS (IQR)	6 (4–8.5)
Median time from admission to EEG (IQR) days	6 (2–18)
Intubated, *n* (%)	28 (80%)
Primary neurologic diagnosis on enrollment, *n* (%)	14 (41%)
Aneurysmal SAH	2 (6%)
Acute ischemic stroke	5 (15%)
Malignant MCA stroke	2 (6%)
Traumatic brain injury	3 (9%)
Spontaneous intracerebral hemorrhage	1(3%)
Anti-NMDA receptor encephalitis	1 (3%)
Acute kidney injury, *n* (%)	10 (29%)

EEG electroencephalography, *GCS* Glasgow Coma Scale, *IQR* interquartile range, *MCA* middle cerebral artery, *NMDA* N-methyl-d-aspartate, *SAH* subarachnoid hemorrhage, *SD* standard deviation

[a] 35 total sonifications were performed on 34 patients. One patient was sonified twice ~ 2 weeks apart for separate episodes of encephalopathy. 12 (35%) patients were postoperative from cardiac surgery at the time of enrollment, 3 (9%) patients were undergoing extracorporeal membrane oxygenation, 1 patient had anoxic brain injury, and 1 patient had fulminant hepatic failure

the one-minute sonification period, and on review of the patient's subsequent visual EEG waveforms, he had a definite seizure about 10 min after the sonification period and 12 min into recording with Ceribell device. In this case, decision to treat changed from "Not Sure" to "Treat." Thus, sonification would have resulted in appropriate treatment of this patient, and he was counted as a true positive. Clinical suspicion (dichotomized to 1–3 = no seizure; 4–5 = seizure) had a sensitivity of 0 (0/2) whereas it was 100% (2/2, CI 0.16–1.0) for handheld EEG. These numbers are too small for the sensitivity estimate to be reliable. Specificity increased from 76 to 85%, a net benefit to 3 patients; overall, five patients (15%) were reclassified properly by sonification of handheld EEG, three without seizures and two with seizures.

In total, 33 cases did not have seizure or rhythmic periodic discharges during the sonification period (Tables 2 and 3). When treatment cases rated as "Not Sure" were included in the "Treat" category (Table 3B), the number of patients who would have been treated unnecessarily with additional medications (based on clinical suspicion alone) decreased from 16/33 (48%) to 7/33 (21%) ($p = 0.01$ by McNemar) after the clinician listened to the patient's EEG. When the "Not Sure" patients were included in the "Not Treat" category (Table 3C), a similar benefit was seen in 7 patients (decrease in unnecessary treatments from 9 to 2, $p = 0.02$ by McNemar). For the two patients needing treatment, handheld EEG changed the decision from "Not Treat" to "Treat" for the one in NCSE, and from "Not Sure" to "Treat" for the patient with "seizure-like" waveform. Outside the sonification window but during subsequent Ceribell EEG recording, two additional patients had definite seizures confirmed by waveform review (Table 4); one patient remained at a suspicion of 1 and a treatment decision of "Not Treat" after sonification, and had a right occipital seizure 7 min into recording which lasted 7 min; the other changed from a suspicion of 3–1, with treatment decision remaining "Not Treat" after sonification, and handheld EEG showed diffuse slowing with a seizure approximately 5 min into recording.

Mean time of Ceribell EEG recording was 56 min compared to 18 h of conventional EEG recording. Of the two patients in whom sonification showed seizure or seizure-like activity, one patient was transitioned to comfort measures prior to conventional EEG, and the other patient was treated with antiepileptic medications after sonification but before conventional EEG, and did not have seizures on conventional EEG. Two patients had negative handheld EEG, but subsequent long-term conventional EEG detected seizures. In one of these patients, 7-min handheld EEG recording revealed no seizures, but subsequent conventional long-term EEG monitoring detected seizures approximately 7 h into recording. In another patient undergoing therapeutic hypothermia, handheld EEG waveform review revealed infrequent generalized polyspike and wave discharges, but the patient's EEG evolved to burst suppression pattern alternating with generalized, high-amplitude ictal bursts consistent with myoclonic status epilepticus. A description of conventional EEG findings is included in Table 4.

Discussion

The current study is a pilot study to provide evidence of the utility of Ceribell's *Brain Stethoscope* function in providing rapid diagnostic EEG information as to the presence of ongoing hemispheric or generalized seizures. Our data from 35 cases in a real-time ICU setting provide preliminary evidence that Ceribell's *Brain Stethoscope* function can help physicians evaluate the presence or absence of non-convulsive status epilepticus by listening to the sound of the EEG at the bedside. Our results indicate that the new handheld Ceribell EEG system reduces time to EEG acquisition and leads to change in management decisions (particularly avoiding unnecessary additional treatment in those who are not actively seizing).

Speed of EEG Acquisition and Ease of Use

The Ceribell EEG System provided rapid acquisition and interpretation of EEG information. The average amount of time it took from arrival of the handheld EEG system at bedside to EEG acquisition by the treating clinician was 6 min, illustrating the simplicity of setup of

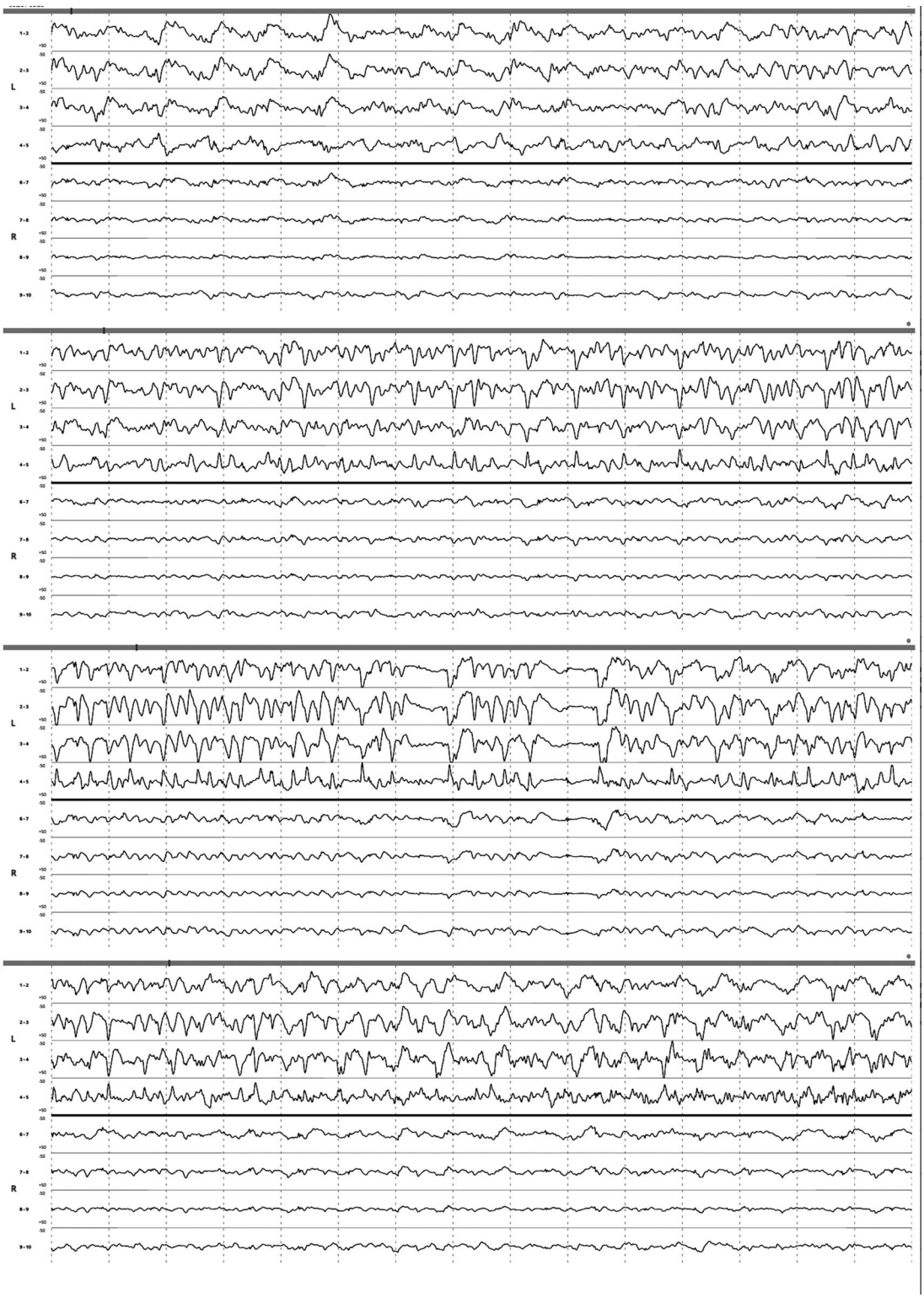

Fig. 3 Visual handheld EEG tracing. One-minute tracing from a patient in non-convulsive status epilepticus (left hemisphere, top EEG channels) identified during sonification. Suspicion for seizure in this patient changed from a pre-sonification value of 1 (very low) to 5 (very high) post-sonification, and treatment decision changed from "Not Treat" to "Treat"

Table 2 Change in clinical assessment pre- vs post-sonification

Suspicion pre-sonification	Suspicion post-sonification[a]		Total
	No seizure	Seizure	
(A) True positives[b]			
No seizure	0	2	2
Seizure	0	0	0
Total	0	2	2
(B) True negative cases[c]			
No seizure	21	4	25
Seizure	7	1	8
Total	28	5	33

[a] Suspicion for seizure (1–5; 1 = very low, 5 = very high) was dichotomized as 1–3 (no seizure) versus 4–5 (seizure)

[b] Sensitivity of clinical suspicion: 0% (0/2, CI 0–84%). Sensitivity of sonification: 100% (2/2, CI 16–100%). 100% improvement in sensitivity, $p = 0.5$

[c] Specificity of clinical suspicion: 76% (CI 58–89%). Specificity of sonification: 85% (CI 68–95%). 9% improvement in specificity, $p = 0.5$

the system; it required little training, and was consistently rated by participating clinicians as easy to use. Often conventional EEG was delayed due to the need for urgent imaging or procedures; given the simplicity and speed of both placement and removal of the Ceribell headband, preliminary EEG information was obtained and treatment initiated before a patient became unavailable for conventional EEG monitoring. Indeed, handheld EEG was able to be obtained for a number of patients in whom conventional EEG was delayed due to the need for imaging, ventricular drain placement, or surgery; in one patient who required emergency surgery, conventional EEG started > 24 h after the initial handheld EEG monitoring had already occurred.

Expedited Access to EEG

Our study demonstrated a mean 86-min reduction in the wait time to EEG using handheld EEG over conventional EEG. While this benefit is already sizable, it likely would have been larger in a real-world clinical setting for a number of reasons. First, we were required to obtain informed consent from each patient's surrogate decision maker prior to placement of the investigational handheld EEG system, which was the largest factor in our time of 23 min from patient identification to placement of the EEG headband. In real-world conditions, the system would be able to be placed immediately. Second, our study occurred only during daylight hours due to research coordinator availability, when EEG technicians were on site and were able to place continuous EEG relatively quickly (median time from order to continuous EEG was 145 min). If the study had been conducted overnight, this difference would undoubtedly have been much larger, due to decreased EEG technician availability at night.

Table 3 Change in treatment decision pre- vs post-sonification

		Treatment decision post-sonification			Total
		Not treat	Not sure	Treat	
(A) Change in treatment decision (as reported) in true negative cases					
Treatment decision pre-sonification	Not treat	17	1	0	18
	Not sure	4	2	0	6
	Treat	6	1	2	9
	Total	27	4	2	33

		Not treat	Treat	Total
(B) Classifying "not sure" as "treat"				
Treatment decision pre-sonification	Not treat	17	1	18
	Treat	10	5	15
	Total	27	6	33
(C) Classifying "not sure" as "not treat"				
Treatment decision pre-sonification	Not treat	24	0	24
	Treat	7	2	9
	Total	31	2	33

The first table contains the treatment decision as rated by the clinician among patients who did not have seizure during sonification. In the second table, the Not Sure patients have been classified as Treat, showing a net reduction in unnecessary treatment to 9 (27%, CI 13–45%) patients ($p = 0.01$) after sonification (15–6). In the third table, the Unsure patients have been classified as Don't Treat, leading to a net reduction in unnecessary treatment in 7 (21%, CI 9–39%) patients ($p = 0.02$)

Table 4 Formal EEG results in all subjects (based on visual review by epileptologists)

Case	Ceribell duration (min)	Ceribell EEG visual review report	Conventional clinical EEG report
1	21	Diffuse slowing with focal seizure in the right occipital region (7 min 23 s into recording)	Moderate diffuse slowing. Generalized rhythmic delta activity with frontal intermittent rhythmic delta activity
2	43	Diffuse slowing with focal right hemispheric seizure that started 12 min 04 s into recording	Moderate to severe diffuse slowing
3	134	Diffuse slowing	Moderate to severe diffuse slowing with low voltage
4	47	Diffuse slowing, missing data from electrode 8 (on bandage)	Severe diffuse slowing with additional right hemispheric slowing
5	8	Diffuse slowing	Severe diffuse slowing
6	25	Rhythmic slowing	Comfort measures instituted prior to conventional EEG
7	7	Diffuse slowing	Mild-moderate diffuse slowing with left frontal epileptiform discharges and 4 electrographic left frontal seizures
8	7	NCSE (LEFT) with diffuse slowing	Comfort measures instituted prior to conventional EEG
9	21	Excessive beta b/s benzodiazepines, otherwise mildly slow	Normal awake and asleep EEG
10	74	Slow bilaterally but with excessive movement artifact specially in the posterior channels	Moderate to severe slowing with bifrontal sharply contoured transients
11	81	Moderate diffuse slowing	Bilaterally diffuse slowing
12	115	Moderate diffuse slowing	Moderate diffuse slowing with Generalized Periodic Discharges
13	93	Moderate diffuse slowing	Moderate to severe diffuse slowing with additional slowing over the right hemisphere and very slow LPDs (Lateralized periodic discharges), bilaterally independent
14	44	Bilaterally dependent generalized discharges and excessive muscle artifact	Myoclonic status epilepticus with intervening burst suppression
15	2	Diffuse slowing	Mild diffuse slowing
16	90	Moderate to severe slowing	Severe diffuse slowing with low voltage
17	33	Moderate diffuse slowing	EEG read unavailable
18	25	Diffuse slowing	Moderate diffuse slowing with additional right frontoparietal slowing and suppression
19	92	Diffuse slowing	Moderate diffuse slowing
20	25	Diffuse slowing with GPDs	Moderate to severe diffuse slowing with episodes of generalized rhythmic slowing (GRDA), and rare runs of non-specific generalized periodic discharges (GPDs)
21	76	Diffuse slowing	Intermittent epileptiform discharges over the left and right frontal regions, less frequently over the bitemporal regions, and sometimes in the form of LPDs (periodic lateralized epileptiform discharges) and mild to moderate diffuse slowing with additional intermittent focal slowing over the right
22	70	Diffuse slowing with triphasic waves	Moderate to severe diffuse slowing, more prominent in the frontal regions, including rhythmic slow patterns with additional intermittent rhythmic slowing and non-specific periodic discharges over the left frontal region
23	18	Diffuse slowing	Moderate diffuse slowing, additional left slowing
24	29	Myogenic artifact, electrode 4 noise.	Diffuse slowing
25	76	Right > left slowing and SIRPID x 1	Moderate to severe slowing with stimulus induced rhythmic waveforms upon noxious stimulation (SIRPIDs)
26	115	Moderate diffuse slowing with sharply contoured waveforms ($L > R$)	Moderate diffuse slowing with brief periods of discontinuities and non-specific blunted generalized discharges, occasionally in runs (Generalized Periodic Discharges, GPDs)
27	33	Diffuse slowing (artifacts in T3-5)	Moderate diffuse slowing
28	117	Mild diffuse slowing	Occasional runs of Generalized Periodic Discharges (GPDs) upon stimulation with moderate diffuse slowing
29	109	Diffuse slowing with seizure 4 min 50 s into recording	Severe diffuse slowing with right temporal electrographic seizure ×1

Table 4 continued

Case	Ceribell duration (min)	Ceribell EEG visual review report	Conventional clinical EEG report
30	111	Diffuse slowing (electrode #2 not connected)	Moderate to severe diffuse slowing with poorly formed bifrontal blunted sharps
31	38	Moderate diffuse slowing	Moderate diffuse slowing
32	102	Alpha coma (left) and slow on right	Semi-continuous irregular diffuse slowing with right sided slowing
33	42	Moderate diffuse slowing	Mild diffuse slowing with occasional sharply contoured, generalized discharges in the initial hours of the recording
34	32	Diffuse slowing	Moderate diffuse slowing
35	11	Diffuse slowing	Moderate diffuse slowing, at times with rhythmic fluctuations

Clinical Evaluation by EEG Sonification

Several methods of EEG sonification have been reported in the literature including the Oxford Medilog System in 1980 prior to the age of digitized EEG [14–20]. These methods rely on off-line compression of the EEG data by a factor of 60 shifting EEG frequencies to audible spectra or mathematical models that generate sound according to the power of EEG signal in a certain frequency band. The Ceribell's sonification method uses brain data (0–100 Hz) as a source of audio signal modulation without distorting its temporal information and without relying on a specific feature of the EEG signal. Listeners hear the brain activity in its own (normal or seizure) state, in its natural time course, and with its rhythms and severity, without breaking down the rich EEG signal to its conventional narrow bands as has been done in prior sonification methods. In a recent analysis of the current method of sonification, EEG-untrained medical students and nurses were able to identify seizures in sonified EEG clips with comparable sensitivity and specificity to expert review of visual EEG display [13]. The real-time nature of Ceribell sonification gives handheld EEG a potential to serve either as a bridge or triage device that provides information on seizures prior to the arrival or availability of an epilepsy-trained neurologist. The EEG information obtained from handheld EEG is available instantly for interpretation by EEG-untrained clinicians at the bedside, as opposed to conventional EEG, which is usually placed by a technician who then has to contact the interpreting epileptologist to review the EEG. None of the physicians in our study were epilepsy-trained, and each clinician underwent only a brief 4-min online training on interpretation of sonified EEG. While all of the treating clinicians in our study were neurology-trained neurointensivists, and thus had some familiarity with EEG interpretation, none of the participating physicians looked at the EEG waveforms during the study, but instead relied solely on listening to the sound of the EEG from each hemisphere, which should increase the generalizability of these results to non-neurologist clinicians.

The Ceribell EEG System changed clinician suspicion for seizure and decision to treat. Ceribell EEG was successful in identifying the one patient who was in NCSE during sonification, and also identified a second patient with an abnormal EEG who went on to have seizures minutes after sonification. While such a small number of patients who had seizure in our sample limit our ability to fully assess the reliability of sonification, these results suggest that sonification with handheld EEG is able to accurately detect seizures. Sonification with handheld EEG also prevented treatment of patients who were not seizing. Depending on whether unsure clinicians would have treated empirically or not, the use of handheld EEG in our study would have prevented treatment of non-seizing patients in approximately 21–27% of our cohort when compared to clinical suspicion alone. The ability of sonified EEG to help avoid inappropriate treatment is significant; it likely avoided unnecessary intubation in one study patient who had multiple clinical events after lithotripsy that did not respond to multiple doses of antiepileptic drugs and benzodiazepines and was about to be intubated for more aggressive therapy. Sonification of EEG in this case revealed no ongoing seizures, and more aggressive therapy was withheld until the EEG waveforms were reviewed formally by an EEG specialist who confirmed the diagnosis of non-epileptic psychogenic events.

It is important to clarify that the question of "Treat" versus "Not Treat" was not about treating or not treating the patient in general. It was a decision to start (the first or give additional) anticonvulsant therapy at the time of sonification because of the presence of ongoing seizures, or to wait for review of the continuous EEG. If sonification did not indicate non-convulsive status epilepticus or seizure-like conditions, then the physicians would decide not to treat until the full EEG was reviewed visually by the neurologist.

Limitations of the Study

Despite the promising results obtained in our study, the major limitation was the short reviews of EEG sounds from one channel on each hemisphere. Thus, visual review of the entire EEG recording would have been more sensitive since in ten patients, the extended review of Ceribell EEG (visual waveforms) identified additional seizures. For these patients, handheld EEG still would have resulted in faster EEG acquisition, and hence, earlier seizure detection than conventional EEG, even if the short sonification period did not capture seizure. Waveform review in these patients resulted in identification of seizures prior to the connection of conventional EEG, which would have been missed otherwise due to the normal time delay in connecting conventional EEG.

Another limitation of our study pertains to the lower specificity of sonification method in differentiating seizure-like conditions (such as rhythmic movements, artifacts, and or periodic discharges) from epileptic seizures. Rhythmic periodic discharges may or may not sound similar to seizures depending on the rhythmicity of the discharges and how repetitive and frequent they are. ICU artifacts such as drip artifact or line noise will be filtered out by the sonification algorithm. With additional training, one might be able to differentiate these conditions from seizures. EEG-untrained users, such as the participants in the current study, were not expected to do so. Frequent repetitive abnormal discharges are heard as sharp fluctuations in tone during sonification, and may be judged as seizure by the bedside clinician, but may not fulfill actual criteria for seizure by an epileptologist. We believe that a high burden of epileptiform activity may warrant treatment since most recent evidence suggests that these waveforms may not be benign and may cause neuronal distress [7]. Indeed, treatment of substantial epileptiform discharges on conventional EEG is sometimes undertaken even if not technically a seizure if the clinician feels it will be beneficial.

Another theoretical limitation of our study is that the EEG headbands consisted of 10 electrodes covering only the lateral surface of the brain. As such, we are mindful that merely focal seizures, especially in the parasagittal regions, may go unnoticed using the reduced-montage EEG. Numerous prior studies have investigated the utility of reduced-montage EEG [21]. Most of these studies used sub-hairline EEG sensors, or montages dissimilar to the one used in the current study. As such, direct comparisons between these prior studies and the current study are limited, as they differ in number of electrodes used, placement, and location (and most of the prior studies were not prospective or within the critical care setting). The electrodes in our study were placed over the hairline and at similar locations as the lateral channels of the conventional 10–20 system. A recent study using the same EEG montage as the one used in our current study found similar accuracy between full and reduced montages (fm-EEG: 95%, rm-EEG: 95%, $p=0.29$). Moreover, neurologists' sensitivity for detecting generalized/hemispheric seizure activity was similar in fm-EEG (100%) and rm-EEG (98%) ($p=0.17$). However, the specificity of rm-EEG for seizures and rhythmic periodic activity was significantly greater (100%) than that of fm-EEG (93%) [21].

Conclusions

Our study was a small pilot study of the Ceribell EEG system, and as such suffered from the limitations inherent to a small sample size, particularly in the assessment of sensitivity. Further studies with a larger cohort of patients will be more informative about the potential utility of sonified EEG in the neuro-ICU setting. Despite its limitations, our study shows that the Ceribell EEG System (including the headband and handheld EEG recording device with sonification algorithm) (1) reliably provided rapid emergent EEG data when compared to conventional EEG, (2) accurately identified subclinical seizures when compared to review on concomitant visual EEG data, (3) resulted in fewer non-seizing patients being treated, and (4) was easy to use by clinicians not trained to place or read conventional EEG.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s12028-018-0543-7) contains supplementary material, which is available to authorized users.

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Author Contributions

All authors contributed substantially to the design and conduct of the study, data acquisition and/or analysis, and revision of the manuscript.

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Compliance with Ethical Standards

Conflict of interest

Josef Parvizi is co-founder of Ceribell. Goodman is on the Ceribell scientific advisory board. Both were involved in the design of the study, commenting on data analysis and interpretation, and revisions of later versions of the manuscript. Other authors have no financial relationship with Ceribell.

Ethical Approval

The trial was approved by our local Institutional Review Board, unique protocol number 38555.

Human and Animal Rights

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national

research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent
Informed consent was obtained from all individual participants included in the study.

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