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FULL-LENGTH ORIGINAL RESEARCH

Detecting silent seizures by their sound

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Summary

Objective: The traditional approach to interpreting electroencephalograms (EEGs) requires physicians with formal training to visually assess the waveforms. This approach can be less practical in critical settings where a trained EEG specialist is not readily available to review the EEG and diagnose ongoing subclinical seizures, such as nonconvulsive status epilepticus.

Methods: We have developed a novel method by which EEG data are converted to sound in real time by letting the underlying electrophysiological signal modulate a voice tone that is in the audible range. Here, we explored whether individuals without any prior EEG training could listen to 15-second sonified EEG and determine whether the EEG represents seizures or nonseizure conditions. We selected 84 EEG samples to represent seizures (n = 7), seizure-like activity (n = 25), or nonperiodic, nonrhythmic activity (normal or focal/generalized slowing, n = 52). EEGs from single channels in the left and right hemispheres were then converted to sound files. After a 4-minute training video, medical students (n = 34) and nurses (n = 30) were asked to designate each audio sample as "seizure" or "nonseizure." We then compared their performance with that of EEG-trained neurologists (n = 12) and medical students (n = 29) who also diagnosed the same EEGs on visual display.

Results: Nonexperts listening to single-channel sonified EEGs detected seizures with remarkable sensitivity (students, 98% ± 5%; nurses, 95% ± 14%) compared to experts or nonexperts reviewing the same EEGs on visual display (neurologists, 88% ± 11%; students, 76% ± 19%). If the EEGs contained seizures or seizure-like activity, nonexperts listening to sonified EEGs rated them as seizures with high specificity (students, 85% ± 9%; nurses, 82% ± 12%) compared to experts or nonexperts viewing the EEGs visually (neurologists, 90% ± 7%; students, 65% ± 20%).

Significance: Our study confirms that individuals without EEG training can detect ongoing seizures or seizure-like rhythmic periodic patterns by listening to sonified EEG. Although sonification of EEG cannot replace the traditional approaches to EEG interpretation, it provides a meaningful triage tool for fast assessment of patients with suspected subclinical seizures.

KEYWORDS

EEG sonification, nonconvulsive status epilepticus, rhythmic periodic pattern, subclinical seizure

1 | INTRODUCTION

Millions of people are seen in emergency departments (EDs) for the evaluation of altered mental status (AMS).[1] Additionally, AMS patients with critical conditions are admitted to intensive care units (ICUs), where a significant portion of these patients are found to have nonconvulsive subclinical seizures.[2] In these patients, electroencephalography (EEG) is the gold standard method for detecting subclinical seizures, especially nonconvulsive status epilepticus (NCSE). A timely diagnosis of NCSE facilitates appropriate acute management and reduces the number of unnecessary diagnostic procedures, length of hospitalization, and morbidity and mortality.[3–5]

The current practice of EEG depends on the interpretation of the acquired data represented in visual or graphical form by specialized neurologists with expertise in reading EEG (clinical neurophysiologists and epileptologists). On visual display, features of the brain waves are often confusing to professionals not trained in reading EEGs. Thus, the current EEG platform does not provide untrained users (especially in the ED and ICU) with instant diagnostic information at the bedside; therefore, the ordering physician not trained in EEG will have to wait until a trained EEG specialist has had time to review the recording. There is often a long delay from the time of EEG order until the ordering physician receives the diagnostic information from the EEG team. One study showed that, for stat EEGs in several university hospitals in North America, the initial interpretation of the EEG had a mean delay of about 3 hours.[6]

In this study, we test the effectiveness of a method by which EEG waveforms are sonified and users hear the sound of rhythmic fluctuations of the waveforms to determine whether the waveforms represent seizures or nonseizures. To this end, we took advantage of recent developments in music research and introduced a novel method of advanced sonification of EEG data. The overarching hypothesis of the study was that users not trained in EEG (such as nurses or medical students) will be able to detect the presence of ongoing seizures by listening to brainwaves converted to auditory form. In other words, the claim is that if a patient is having ongoing seizures (for example NCSE), one will be able to appreciate the presence of seizures by listening for only a few seconds to the sound of the patient's brainwaves. Like auscultating the sound of the heart with a stethoscope, one can auscultate the tone of the brain to determine whether the patient is seizing at that very moment. Lastly, the aim of the study was not to test whether users without prior exposure to EEG could differentiate seizures from seizure-like rhythmic periodic patterns such as generalized periodic discharges (GPDs) or lateralized periodic discharges (LPDs), because even individuals with extensive EEG training will often disagree on the nomenclature and will have difficulties in identifying subtle differences among these conditions.[7]

Key Points

- We examined the effectiveness of a novel method of EEG sonification for detecting subclinical seizures
- Medical students and nurses detected seizures with >95% sensitivity after listening to 15 seconds of sonified EEG
- Medical students and nurses also could differentiate seizures and seizure-like rhythmic periodic discharges from those without these abnormalities with >80% specificity

In our current study, we explored the performance of our sonification method when used by medical students and nurses compared to the performance of trained epileptologists reviewing the same samples on visual display.

Our findings confirm that individuals without EEG training can detect ongoing seizures or seizure-like rhythmic periodic patterns by merely listening to a short duration of sonified EEG. Although sonification of EEG cannot replace the traditional approaches to EEG interpretation, it provides a meaningful triage tool for fast assessment of patients with suspected subclinical seizures.

2 | MATERIALS AND METHODS

2.1 | Standard protocol approvals

This study was conducted with the approval of the Stanford University Institutional Review Board and in accordance with the Standards for Reporting Diagnostic Accuracy Studies (STARD) guidelines.

2.2 | EEG sample selection

We selected 84 EEG samples (15 seconds long) from recordings obtained in the routine evaluation of patients with altered mental status. Although it is unusual to ask someone to evaluate only 15 seconds of the EEG, the 15-second-long EEGs were chosen because they correspond to a single page of EEG on visual display. Also, the users were not allowed to change the gain or filter settings, because we wanted to ensure that all raters provided their responses on the basis of the same data.

The original epileptologist's interpretation report was used to identify EEGs that captured findings commonly seen in the ICU, including seizures, seizure-like rhythmic

and periodic patterns (eg, GPDs and LPDs), nonseizure patterns such as slowing, and normal activity. In our selection of seizure cases, we made sure that the cases were chosen from patients who had no clinical signs associated with the seizures, hence the terms "silent," "nonconvulsive," or "subclinical." We reviewed each continuous EEG record to extract a 15-second epoch representative of the activity noted in the original epileptologist's report. Figure 1 shows examples of each condition.

The relative number of files for each category was chosen according to the reported prevalence of such cases in the literature.[4,8] We also emphasize that the percentage of nonseizure cases far exceeded the percentage of seizure cases. Therefore, high performance in detecting seizure cases could not be explained by chance performance.

2.3 | Reference standard

Three senior epileptologists, each with >10 years of EEG experience, reviewed each 15-second EEG sample presented visually in standard double banana montage. We defined samples as seizures (n = 7), seizure-like abnormalities (eg, GPDs, LPDs, triphasic waves, burst suppression, n = 25), and slowing or normal (n = 52) based on the majority agreement of these 3 experts.

2.4 | Study design

Two surveys were conducted, one using an 18-channel visual presentation of EEG samples and a second using audio presentations of single channels from the left (T3-T5) and right (T4-T6) hemispheres from the same EEG

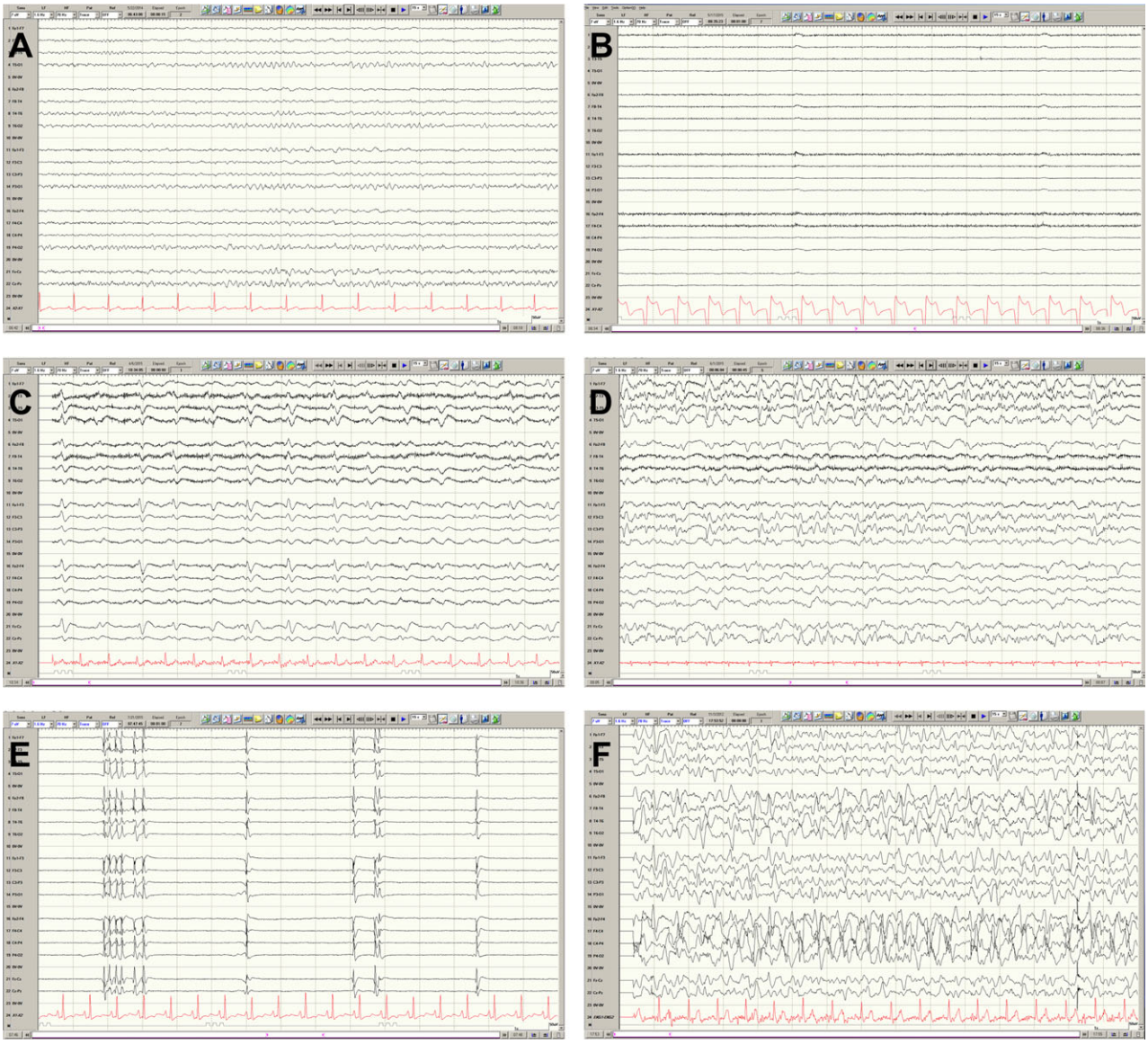

FIGURE 1 Examples of electroencephalographic (EEG) samples with their sound. Examples are shown of EEG conditions used in the current study: A, normal; B, slow; C, generalized periodic discharges; D, lateralized periodic discharges; E, burst suppression; and F, seizure

samples prepared using our proprietary sonification algorithm described elsewhere. Samples were presented in a random order in both surveys. Visual samples were presented as one static page, whereas in the audio survey the sound clips from left and right channels were presented separately. Prior to completing the audio survey, participants watched a short video that described the appearance of seizures and seizure-like patterns (eg, GPDs, LPDs, triphasic waves, burst suppression) on visual display and the correlation of specific visual features that define these patterns (rhythmicity and periodicity) with the sound of these brainwaves after sonification.

2.5 | Study participants

We recruited 15 neurologists with EEG training (ie, epileptologists, epilepsy fellows, senior neurology residents), 34 medical students, and 30 nurses at Stanford University Medical Center to participate in the audio and visual EEG surveys. Of the 15 neurologists, 12 completed the visual EEG survey and 3 served as referees; of the 34 medical students who completed the audio EEG survey, 27 also completed the visual EEG survey. The 30 nurses participated only in the audio EEG survey.

2.6 | Sonification method

We used a novel sonification algorithm to translate the low-frequency EEG signals into the audible range by using them as modulators of a voicelike synthesized sound.[9] EEG signals acquired from 1 temporal channel (T3-T5 or T4-T6) were applied as modulators of the synthesized sound. For each visual EEG record, we produced 2 sonified EEG clips (1 from each hemisphere). Using the sonification method, vocal pitch, loudness, and formant structure were directly varied by the input signal. In the seizure case, the sonification renders epileptic spike trains into speech-like declamations with a loud, strong rhythmic character, which is easily distinguished by ear from the quieter, slower, and smoother-sounding normal case (see Appendix S1). The unique feature of this new sonification method is in its ability to use brain data (0-100 Hz) as a source of audio signal modulation without distorting its temporal information. Listeners hear the brain activity in its own state (normal or seizure), 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.[10–12]

2.7 | Data coding

For each EEG sample in the visual survey, participants were asked to indicate the presence of any and all specific findings (seizure, GPD, LPD, triphasic wave, burst suppression, slowing, normal, or other). We reviewed participants' responses (including those entered as free text if the participant selected "other") and coded their selections of specific findings as indicating "seizure" (if they indicated seizure activity was present, regardless of other selections) and "seizure or seizure-like" activity (if they indicated seizure, GPD, LPD, triphasic wave, or burst suppression was present).

For each single channel presented in the audio survey, participants were asked to judge whether the sound represented seizure or nonseizure (respondents were also able to respond "I do not know"). The visual EEG displays could be rated as "seizure" if the neurologists noticed seizure activity in any of the EEG channels. In the audio survey, the left and right channels were presented separately, and for each EEG sample we had 2 responses, which were then combined for patient-based analysis; if a participant responded "seizure" for either channel, the response for the EEG sample from that patient was coded as "seizure." This resulted in an equal number of averaged responses across visual and audio surveys.

2.8 | Statistical analysis

For each of the respondents (who were not part of the reference standard), we calculated the sensitivity and specificity of both visual and audio EEG for determining the presence of seizure and of seizure/seizure-like activity when compared to the reference standard. These analyses were conducted at the sample level (rather than for individual channels presented in the audio survey). Differences between diagnostic statistics (reported as mean with 95% confidence intervals [CIs]) associated with display modality (audio vs visual) and training level (physician vs nurse vs student) were calculated using 2-sample t tests; a significant level of $\alpha = .05$ was used with Bonferroni correction for multiple comparisons.

3 | RESULTS

The STARD flow diagram is shown in Figure 2. The neurologists with EEG training who completed the visual survey included 7 epilepsy fellows and 5 neurology residents. No significant differences in diagnostic statistics were observed between neurologists of different levels of training (attending, fellow, and resident) or between untrained individuals (nurses and students).

Review of visual EEG is the gold standard method for detecting seizure activity. However, there are reports of significant interrater variability among EEG readers and the method is neither 100% sensitive nor 100% specific, even

when read by trained physicians.[13–16] We confirmed this by showing visual EEG samples to EEG-trained epilepsy fellows and neurology residents, who detected seizures with only 86% sensitivity (CI = 79%-93%) and 87% specificity (CI = 84%-90%), and seizures/seizure-like activity with only 88% sensitivity (CI = 86%-90%) and 90% specificity (CI = 84%-95%; Figure 3). By contrast, untrained individuals (medical students and nurses) demonstrated surprisingly high sensitivity for seizures and specificity for seizures/seizure-like activity while listening to the sound of EEG. Their performance using audio EEG was comparable to that of neurologists with EEG training (Figure 4). The sensitivity for seizures observed for students and nurses was 98% (CI = 96%-100%) and 95% (CI = 90%-100%), respectively, whereas their specificity for seizures was 65% (CI = 61%-69%) for nurses and 66% (CI = 63%-69%) for students. When considering responses indicating the presence of seizure as correct for both seizure and seizure-like samples, specificity increased to 82% (CI = 78%-86%) for nurses and 85% (CI = 82%-88%) for students. Sensitivity for seizures and seizure-like activity was 77% (CI = 72%-81%) for nurses and 79% (CI = 77%-82%) for students. Nurses and students detected seizure-like events with 77% and 79% sensitivity and 82% and 85% specificity, respectively. Despite their high performance using audio EEG, students, as might be expected, were less able to make accurate diagnoses using visual EEG. They demonstrated 76% sensitivity (CI = 69%-83%; $P < .001$) and 65% specificity (CI = 58%-73%; $P = .92$) for seizures and 62% sensitivity (CI = 54%-70%; $P < .001$) and 65% specificity (CI = 57%-72%; $P < .001$) for seizures and seizure-like activity. As shown in Figure 5, medical students who had taken both the visual and audio tests demonstrated greater and more consistent sensitivity and specificity for seizures and seizure-like activity by listening to EEG sound.

4 | DISCUSSION

EEG is the current gold standard method for monitoring the brain's electrophysiological activity. Traditional approaches to interpreting EEG have mostly involved visually inspecting the electrical signals in polygraph-style charts. This approach is useful for determining the approximate source of electrophysiological abnormality (eg, focal seizures), but it has proven to be impractical in critical settings where there is an urgent need to assess patients with AMS who may be having ongoing subclinical nonconvulsive seizures.

We have invented a new way of evaluating EEGs by which clinical team members, including nurses and more junior trainees, can instantly assess whether a patient is having seizures by listening to the EEG sound, that is, the "brain stethoscope function" (see Appendix S1 for sample sounds). Our continuous modulation technique[9] runs in real time and is computationally inexpensive. It creates a distinctive sound that clearly contrasts seizure versus nonseizure brain states. If there are no seizures, the listener hears a steady vocal tone with no variation. If there are seizures, fluctuations in the EEG signal cause frequency

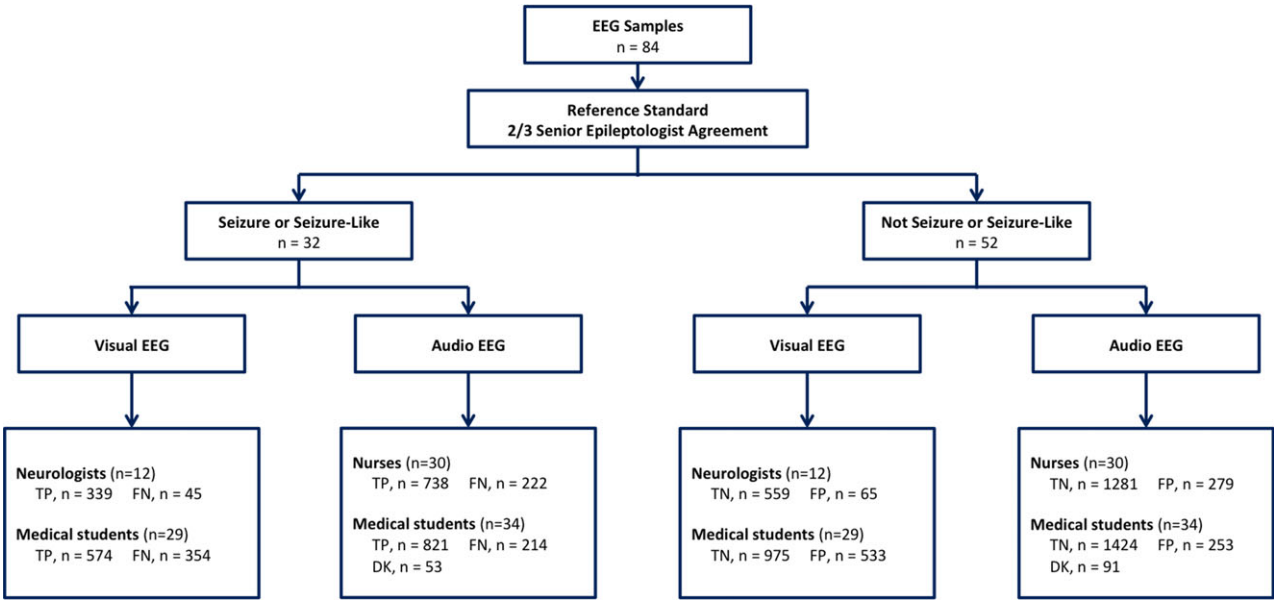

FIGURE 2 Standards for Reporting Diagnostic Accuracy Studies flow diagram. We used 84 electroencephalographic (EEG) samples in the current study, and responders' ratings of the EEGs were compared to reference standard, which was the majority agreement of 3 epileptologists. DK, do not know; FN, false negative; FP, false positive; TN, true negative; TP, true positive

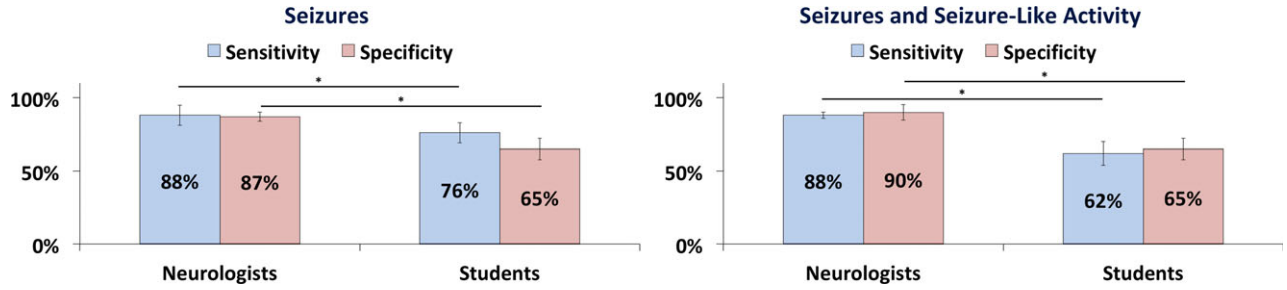

FIGURE 3 Visual electroencephalographic (EEG) results. Sensitivity and specificity are shown of visual EEG for seizures (left) and seizure/seizure-like activity (right) when read by neurologists and medical students. Asterisks denote $P < .05$. Error bars represent 95% confidence intervals

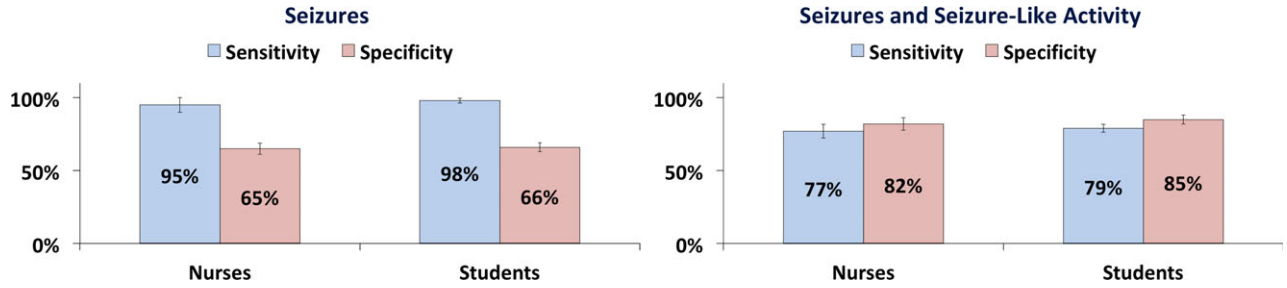

FIGURE 4 Audio electroencephalographic (EEG) results. Sensitivity and specificity are shown of audio EEG for seizures (left) and seizure/seizure-like activity (right) when read by nurses and medical students. Statistical differences between neurologists, nurses, and students did not reach statistical significance. Error bars represent 95% confidence intervals

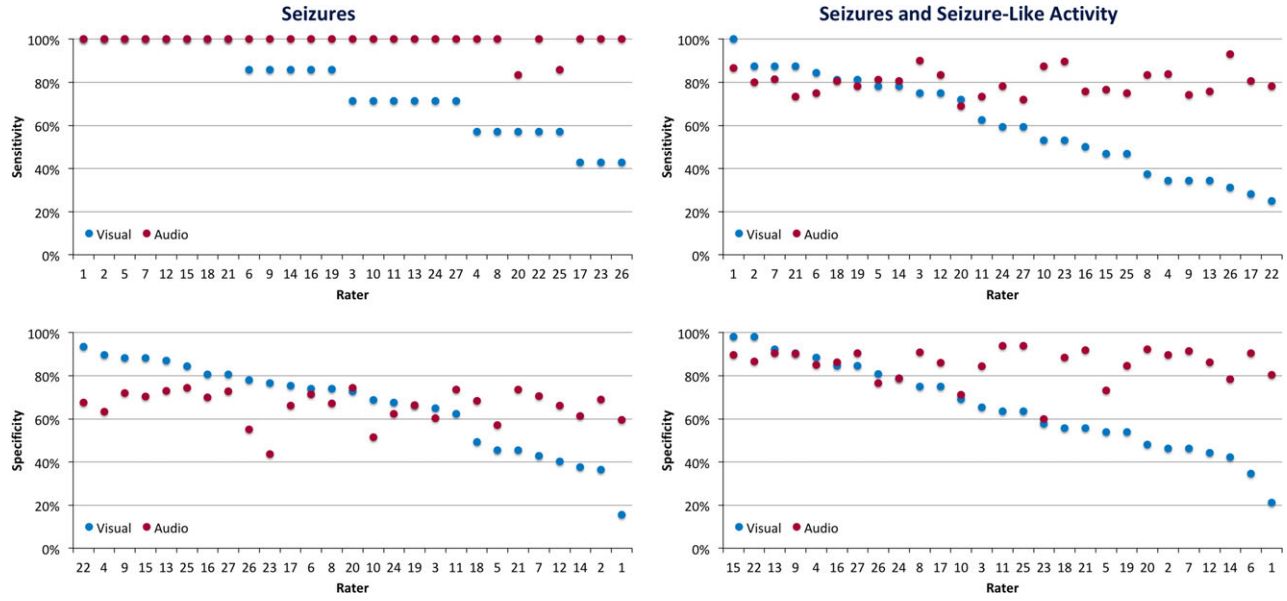

FIGURE 5 Comparison of medical student performance using visual and audio electroencephalograms (EEGs). Medical student (n = 27) detection of seizures (left column) and seizures and seizure-like activity (right column) by visual inspection (blue) versus listening to sonified EEG (red) demonstrates variable performance using visual EEG but consistently high performance using audio EEG

fluctuations in the tone, an effect very much like vibrato. In the current study, we confirm that individuals without EEG training can detect ongoing seizures or seizure-like rhythmic and periodic patterns by merely listening to short clips of sonified EEG. Our method of listening to the "sound of the brain" is similar to listening to the sound of the heart with a stethoscope. We move the stethoscope to different locations of the chest to listen to different valves

of the heart. Similarly, with EEG sonification, a user can listen for a few seconds to the sound of any part of the brain by choosing the appropriate EEG channel and the hemisphere.

Ours is also the first study to test the capability of a sonification method to detect a range of significant abnormalities when it is used by clinical staff (eg, physicians, nurses, and students). Although sonification of EEG cannot replace the traditional approaches to EEG interpretation, especially when it concerns detection of single epileptiform discharges, it seems to be ideal for fast assessment of patients with ongoing subclinical seizures. The less-than-perfect specificity of audio EEG for seizures and improved specificity for the broader category of seizure/seizure-like activity suggest that nonexperts (and even experts) may not be able to differentiate subtle differences between generalized rhythmic and periodic patterns (eg, GPDs and triphasic waves) and status epilepticus by their sound. It is often difficult even for trained EEG specialists to differentiate triphasic waves from NCSE when reviewing visual EEGs.[14,17] Therefore, the sonification method should be used as a triage diagnostic tool to help nonexpert users discern normal or slow activity from seizures and grossly abnormal seizure-like rhythmic or periodic discharges.

Our results strongly suggest that EEG sonification can have a meaningful application in rapid response settings when EEG interpretation is crucial in making treatment choices. Sonification methods prior to the digitization of EEG systems showed great promise in accurately diagnosing seizures. One such sonification method used by the Oxford-Medilog 9000 System in the early 1980s demonstrated excellent capability to detect seizures in long-term ambulatory EEGs recorded on a tape by playing it at $\times 60$ speed.[18] Although this method was useful for offline review of long-term EEG files, the compression of EEG by the factor of 50-200 distorts the temporal information and does not allow bedside monitoring in real-time. Unlike other existing sonification algorithms, our method preserves the temporal features of the EEG as the users listen to the sound in real-time, as if they are listening through a brain stethoscope. Preserving the natural flow of EEG signal in time may have, in part, enabled the users to detect seizures and seizure-like activity with remarkably high sensitivity and specificity.

Lastly, we are mindful of the limitations of our study's retrospective design. We had selected representative EEG samples for sonification as opposed to prospectively recruiting patients and studying clinicians' interpretation of the EEG sounds in real time and at the bedside. We are also mindful that our method selects individual channels (T3-T5 or T4-T6 in this study) for sonification, and any focal seizures in other channels (that do not cause changes in the selected temporal channels) may go undetected. However, because the intended use of EEG sonification is to detect generalized or hemispheric patterns such as the ones in cases of NCSE, single-channel sonification may be sufficient. However, this needs to be tested in prospective studies. Clinical trials using EEG sonification at the bedside are currently underway.

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DISCLOSURE OF CONFLICT OF INTEREST

J.P. and C.C. are inventors of the sonification method used in this study and cofounders of Ceribell, a startup company that has licensed the technology from Stanford University. K.G. and B.R. have no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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