Toward high-throughput, non-invasive seizure detection using piezoelectric motion sensors

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NEUROSCIENCE 2019

Introduction

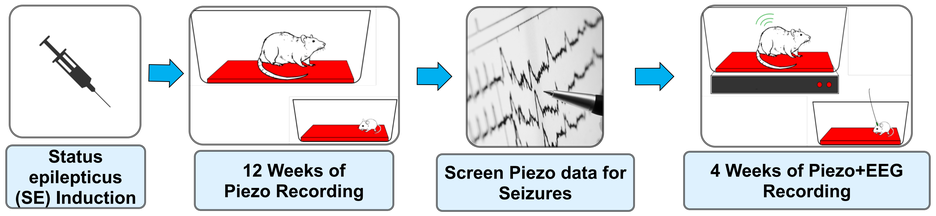
Epilepsy is a neurological condition characterized by spontaneously recurring seizures, and affects an estimated 65 million individuals worldwide. Preclinical models play a vital role in the development of therapeutic strategies. However, assessing experimental outcomes in these models requires quantification of the seizure burden, and how it varies with treatment. With spontaneously recurring seizures, this requires continuous, weeks to months of data collection and periodic screening (usually by manual review of recorded video) to identify seizure occurrence. This is a very tedious process, and consumes a great deal of time and effort.

Our objective here is to develop tools for seizure detection using non-invasive piezoelectric (piezo) technology that can be easily scaled to accommodate high throughput experiments. In this initial investigation, we set out to answer the following questions:

1. ***Can non-invasive sensors be used to efficiently screen large datasets for spontaneous seizures?***
2. ***Can we detect epileptogenesis at its onset and identify when animals have stable seizure yields?***
3. ***Do detections correlate with seizure onset and dynamics as identified by the EEG?***

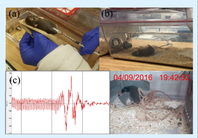
Methods

All procedures were performed with prior IACUC approval at the University of Kentucky.



1. Induction of Status Epilepticus (Acute Seizures)

a. Administer pilocarpine
b. Monitor and score seizures on Racine scale.
c. Transfer animals that had seizures to Piezo cages

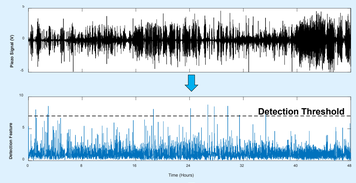


2. 12-Week Piezo Monitoring of Epileptogenesis

- 12 C57BL/6 mice (6-8 wks); 7 Wistar (2-3 m.o.) rats transferred to Piezo cages
- Piezo sensor under cage floor to track behavior
- Around-the-clock 12-week recording

3. Non-invasive Screening of Spontaneously Recurring Seizures

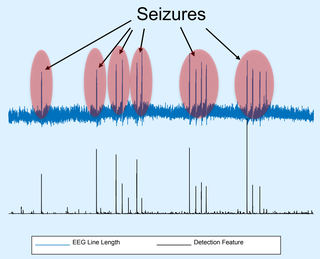
Raw data was exported to European Data Format (EDF), and processed using MATLAB. Weekly piezo recordings were segmented into 1-second epochs, within which a line length signal feature was computed and tracked to detect large deviations from a moving background. Candidate seizure detections were verified via a video record.



Detection Time	Observation	Seizure Onset
6/20/2019 1:28:41	Grooming	-
6/21/2019 22:24:13	S4 Seizure	22:23:53
6/22/2019 18:02:57	S5 Seizure	18:02:48
6/22/2019 23:12:25	S5 seizure	23:12:01
6/23/2019 21:21:33	Myoclonic Twitches	-
6/24/2019 2:03:09	S4 seizure	02:02:49
6/24/2019 5:04:05	S5 seizure	05:03:49
6/24/2019 15:37:09	S5 Seizure	15:36:57
6/24/2019 17:22:21	Grooming	
6/24/2019 21:24:21	S4 Seizure	21:24:11

4. Validation of Seizure Detection via EEG/EMG

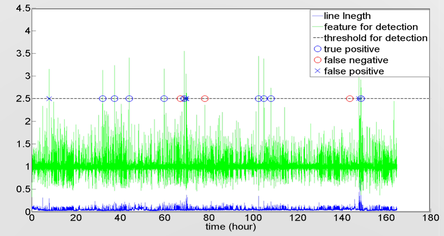
To validate the piezo detections, a subset of the animals that showed high seizure yield (6 mice, 2 rats) were instrumented with EEG/EMG and recorded for an additional 4 weeks. Timestamps of seizures verified on the EEG were compared to timestamps from the piezo-based detector. By varying the threshold and estimating performance metrics, a profile of the algorithm's potential was constructed.



Results

Proof of Principle Investigations

Figure 1: Sample of piezo based seizure detection in mice. Detections flagged when the detection feature (green) crosses specified threshold (black dash). Detections compared against EEG-verified seizure onset times and marked accordingly.



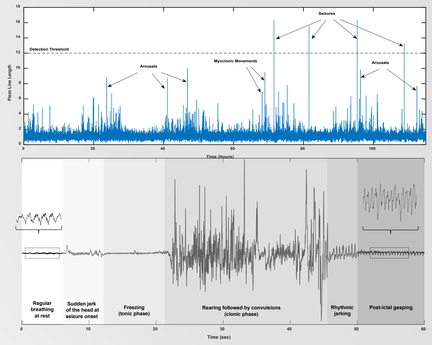


Figure 2: Application of piezo system to seizure screening in rats. After positive results in mice were observed, 4 rats previously subjected to SE induction with pilocarpine were placed in piezo cages and recorded for 8 weeks. While high precision (low number of false positive detections) was observed, the lack of EEG barred us from determining the true number of seizures – motivating a more thorough investigation in rats.

Non-Invasive Tracking of Epileptogenesis and Seizure Screening

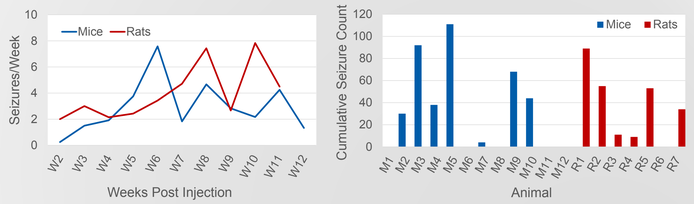


Figure 3: Utility of the piezo system in high-throughput epilepsy screening. 11 weeks of data from 19 animals (12 mice; 7 rats) were screened non-invasively to identify animals having seizures. A relatively selective threshold (40 detections/week) was used, which yielded a recall of ~30% for weeks containing seizures. Verified seizures could be used to build a population profile of epileptogenesis **(left)** and identify which animals were best suited for EEG instrumentation **(right)**.

Validation of Piezo Detection via EEG Seizure Identification

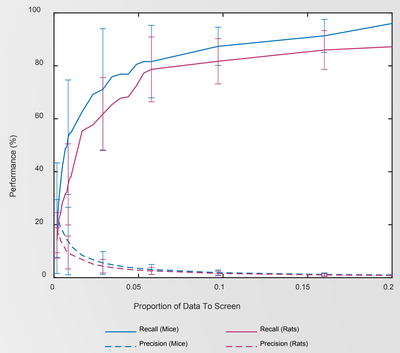


Figure 4: Effect of detection threshold on performance. For each animal, one week of data during which at least 10 seizures were observed was selected for Piezo detection validation. Recall reached values over 90%, but at the cost of low precision. However, a respectable 70% of seizures can be detected with a less aggressive threshold, ***that requires review of under 5 hours of candidate detection data per week (4% of the total). 40% of all seizures*** can be identified in one hour of detections. The number of seizures for mice and rats were 153 and 121 respectively.

Parallels between Piezo and EEG Measures

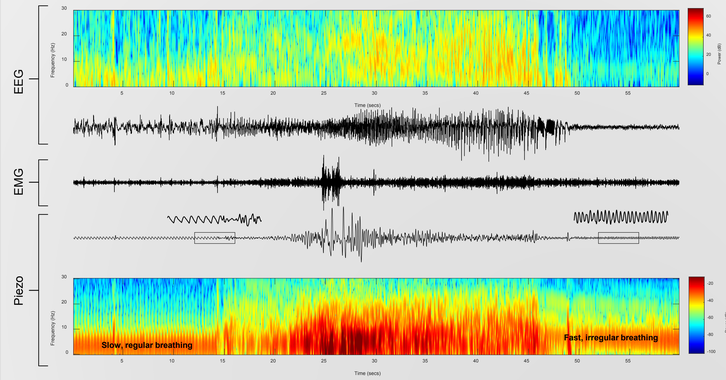


Figure 5: Example of temporal dynamics of piezo signal during seizure. Regular breathing in sleep is interrupted at seizure onset (t = 15 sec). As the seizure evolves (see EEG), seizure-related behaviors translate to changes in the piezo signal. Piezo signal dynamics mirror those seen in the EMG, but with additional information related to rhythmic behaviors (see Figure 2, bottom), including post-ictal changes in breathing (Figure 5, bottom).

Conclusions

- Applying simple detection methods to piezoelectric sensor output was successful in detecting seizures non-invasively
- Data could be screened much faster than through conventional video review (< 6 hours of candidate data to review one week)
- Detection onsets were in close proximity to EEG onsets (~4 sec latency)
- The threshold-based novelty detector used here has limitations and warrants further development

Future Directions

- Incorporate additional features to increase detection sensitivity/specificity
- Address factors affecting detection: cross-talk with other cages, ambient noise, etc.
- Explore other algorithms for detection
  - Supervised classifiers, matched filters, etc.
- Incorporate additional sensors and configurations
- Expand testing to other epilepsy models (e.g., SCN8A, Lafora disease)

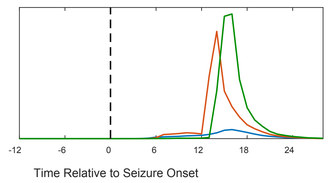


Figure 6: Example templates of characteristic detection feature dynamics seen during seizures. A characteristic trend unique to seizures could be harnessed to increase detection accuracy.

Acknowledgments

Support: This work was made possible by NIH Grant No. NS107148 and by seed funds from the University of Kentucky Epilepsy Research Center (EpiC).
COI Disclosure: K. Donohue and B. O'Hara have ownership stake in Signal Solutions, LLC; D. Huffman is currently an employee of Signal Solutions, LLC.

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