Noninvasive Seizure Screening in Preclinical Models of Epilepsy

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Rationale:
Animal models are widely used to investigate the neurophysiology of epilepsy and titrate experimental therapies. The pilocarpine mouse model exhibits many of the hallmarks of human limbic epilepsy including morphological changes in the hippocampal formation, a latent period followed by intermittent and spontaneous seizures, and comorbid effects on sleep and cognition. Those working with such models typically monitor the animal during the latent period, which can last for weeks, hoping to observing seizures prior to EEG implantation. A stable seizure rate may then need to be documented prior to experimentation. These factors highlight the need for a noninvasive automated method that would enable detection of early-stage seizures and estimation of seizure rate before invasive EEG implantation and experimentation. We have previously shown how vigilance state can be scored noninvasively in mice using a floor-mounted piezoelectric motion sensor. Here, we assess the feasibility of noninvasive seizure detection in pilocarpine-implanted mice using this "piezo" sensor.

Methods:
All procedures were conducted with IACUC approval. Five adult male wild type mice (C57BL/6, Harlan) were treated with pilocarpine i.p. and instrumented with EEG/EMG. After recovery, continuous recording of EEG, EMG, piezo and video was initiated and 160 seizures with overt behavior (rearing, loss of posture) were verified in 35 days from the EEG and video. A line length metric (LL) was computed from the piezo signal in 1s windows and the ratio with respect to an exponentially smoothed reference value used for seizure detection by comparing against a preset threshold determined from training data. The detections were verified against EEG to assess the detector's sensitivity (proportion of true seizures detected) and precision (proportion of correct detections).

Results:
A five-fold cross-validation scheme (four mice for training and one for testing in each fold) was employed to assess the accuracy and robustness of noninvasive seizure detection. The detection threshold was optimized on the training data to give a sensitivity of 90%. On cross-validation, the detector produced a mean sensitivity of 87.7% and a mean specificity of 28.6%. The thresholds deviated by less than 6.5% from their mean.

Conclusions:
The noninvasive seizure detection method described above shows both promising and stable performance. While the performance was biased in favor of high sensitivity, this was by design, since we can expect to discover nearly 90% of all seizures without having to visually verify more than three or four times as many detections. This is a minor inconvenience, considering the alternative of having to review several days of data to find a handful of genuine events. The method is therefore expected to be immensely useful to researchers working with preclinical models of epilepsy.