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Title: Multi-taper spectral analysis of stimulation artifact and epileptiform seizure entrainment data

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Content:

RATIONALE:
Low-frequency electric fields (<<100Hz), unlike pulsed stimulation, have a graded, modulatory effect on neural activity and minimal recording artifact when properly instrumented. As a first step in developing a chronic feedback seizure control system based on low frequency modulation, we here demonstrate from spontaneous seizures in the tetanus toxin model of temporal lobe epilepsy, that field potential spikes are transiently phase-locked with ongoing open-loop sinusoidal field stimulation. Accurate stimulation artifact removal and characterization of field potential spike entrainment are achieved with modern multi-taper spectral analysis tools.
METHODS:
All procedures were approved by the IACUC. Tetanus toxin (5ng/uL) was implanted in the right ventral hippocampus of Sprague-Dawley rats (n=4). A stimulation electrode pair was inserted to straddle the arc of the ventral CA3, along with bipolar hippocampal depth and cortical screw electrodes for EEG. Spontaneous seizures were observed within a week, peaking at ~30/day in weeks 2-4. After a baseline recording period, open loop sinusoidal stimulation (0.5–25Hz) was applied in a 1hr on/off duty cycle. Spectral analysis methods were used to determine the transfer function between the applied stimulus current and recorded artifact. A 3rd order IIR filter was then created to match the transfer function for artifact subtraction and tested both in vitro and in vivo. Seizures were detected by surges in 5-25Hz EEG power, and field potential spike times were identified by geometrical features. 150s windows of data starting 30s before seizure onset were analyzed. The seizures were characterized as point processes based on spike times. Thomson's F-test for spectral lines was applied to non-overlapped 4s windows (frequency resolution=0.25Hz) (Jarvis and Mitra Neural Comp. 2001). The number of windows with a significant line at the stimulation frequency quantifies entrainment. The number of stimulated seizures at each frequency with one or more significant windows was tested for significance and compared to observed lines at other frequencies and for unstimulated seizures.
RESULTS:
Artifact removal is achieved with high fidelity. Significant EEG spike entrainment (mean~12s,p<0.01) during seizure was observed at locations ipsilateral and contralateral to stimulation for 44/112 seizures at several frequencies (3,11,14,15,17,20 Hz) in 3/4 animals. In the fourth, limited but significant entrainment (4-8s in 3/31 seizures, p<0.01) was observed at 15Hz alone ipsilateral to stimulation. In this case, histology showed that the stimulation electrode was slightly outside the arc of the CA3.
CONCLUSIONS:
Neural recording during low-frequency electric field modulation has been demonstrated in chronically implanted animals. Entrainment of field potential spikes during seizure was observed bilaterally in response to periodic low frequency (<25Hz) sinusoidal stimulation. This is a significant step in the implementation of closed-loop seizure control using low frequency electrical fields. (Support: NIH grants R01EB001507, K02MH01493, and R01MH50006.)