THE UNIVERSITY OF RHODE ISLAND
COLLEGE OF ENGINEERING

Toward a noninvasive automatic seizure control system with transcranial focal stimulations via tripolar concentric ring electrodes

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THINK BIG WE DO℠

Introduction

- Epilepsy is a neurological disorder that affects approximately one percent of the world population and in about one third of patients antiepileptic drug therapy is ineffective.
- Noninvasive electrical brain stimulation has recently shown potential for additive seizure control therapy but the best structures to stimulate and the most effective stimuli to use are still unknown.
- Concentric ring electrodes (CRE) perform the second spatial derivative, the Laplacian, on surface potentials.

- tEEG, Laplacian encephalography (EEG) with the tripolar CRE (TCRE), is superior to conventional EEG with disc electrodes in: spatial selectivity, signal-to-noise ratio, localization, approximation of the analytical Laplacian, and mutual information [1]-[3].

[1] Besio et al. (2006) *IEEE Trans. BME.*, 53(5): 926-33
[2] Besio et al. (2006) *Ann. Biomed. Eng.*, 34(3): 426-35
[3] Koka and Besio (2007) *J. Neurosci. Meth.*, 165: 216-22

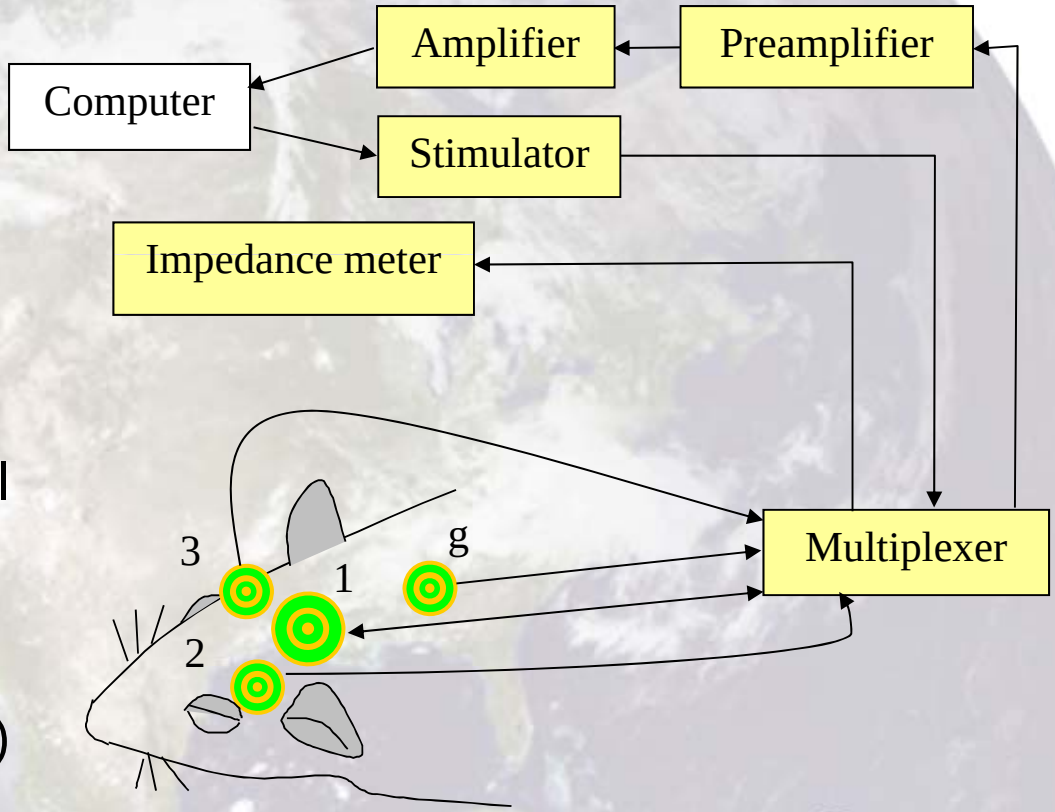
Introduction

- Electrical stimulation via the CRE has a much more uniform current density and focuses the stimulation directly below the electrodes – therefore, transcranial **focal** stimulation (TFS).
- TFS via TCRE have been previously shown to attenuate acute seizures in three seizure models: induced by pilocarpine [1], penicillin [2], and pentylenetetrazole (PTZ) [3].
- As the next fundamental step, we use TFS via TCRE on the scalp of rats after inducing seizure with PTZ to assess:
  - The effect of TFS on behavioral and electrographic seizure activity;
  - The potential of TFS to be used for automatic seizure control.

[1] Besio et al. (2007) *Epilepsia*, 48(12): 2273-9
[2] Besio et al. (2009) *Epilepsy Behav.*, 16(1): 3-46
[3] Besio et al. (2011) *Int. J. Neural. Syst.*, 21(2): 139-49

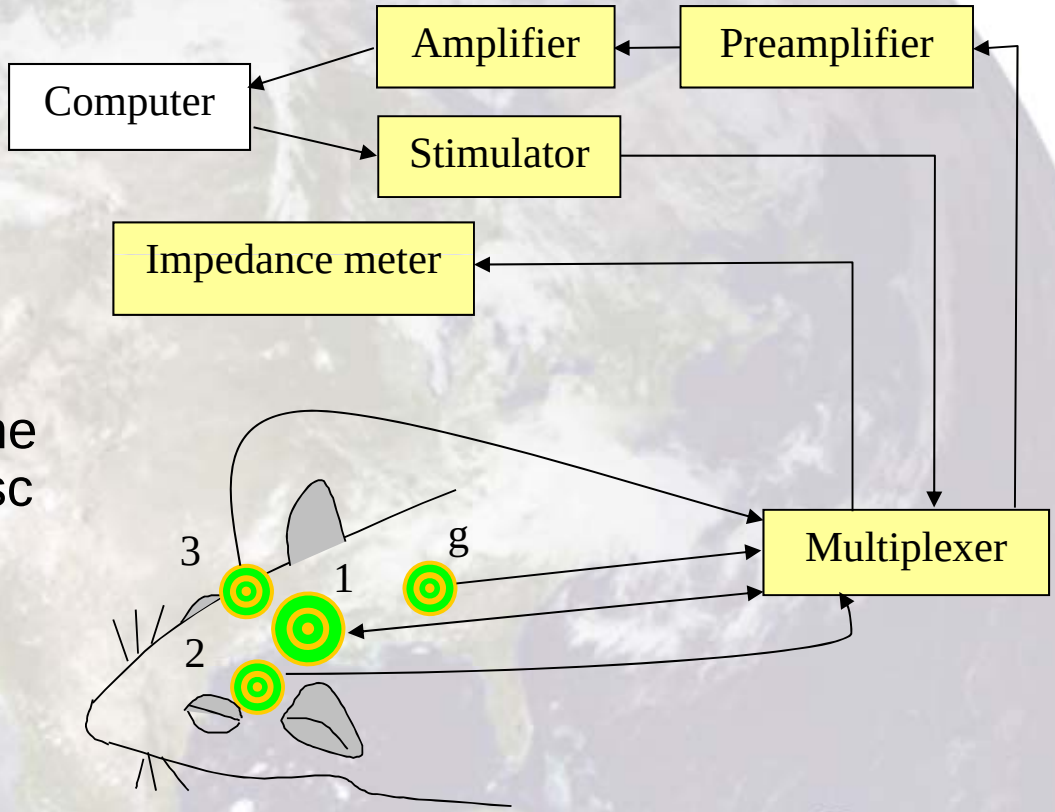
Introduction

- Adult male Sprague-Dawley rats were used.
- Four custom TCREs were placed on the scalp with conductive paste and adhered with dental cement 24 h before the experimental procedure.
- TCREs (1-3) were used for recording. Shorted TCRE (g) was the isolated ground.



Introduction

- Multiplexer was used to switch TCREs between 3 modes: recording (tEEG), stimulation (TFS), and impedance measurement.
- The TFS (300 Hz, 50 mA, 2 min) was applied between the outer ring and the central disc of TCRE (1).
- Division into groups (TFS treated and control) was based on skin-to-electrode impedance for TCRE (1).



Behavioral activity

- Preliminary results showed that TFS caused a significant reduction in duration of myoclonic activity for two independent groups of animals: PTZ was administered to animals in both groups once with only the TFS-treated group receiving TFS triggered manually after the first myoclonic jerk (MJ) but not the control group [1].

- Expansion of analysis:
  - Four different metrics were used (3 of which could potentially be affected by TFS);
  - Different experimental design: PTZ (45 mg/kg i.p.) was administered to the animals in both groups twice (one week apart) with only the TFS-treated group receiving TFS after the second PTZ administration only.

[1] Besio et al. (2010) *Epilepsia,* 51(3): 85-85.

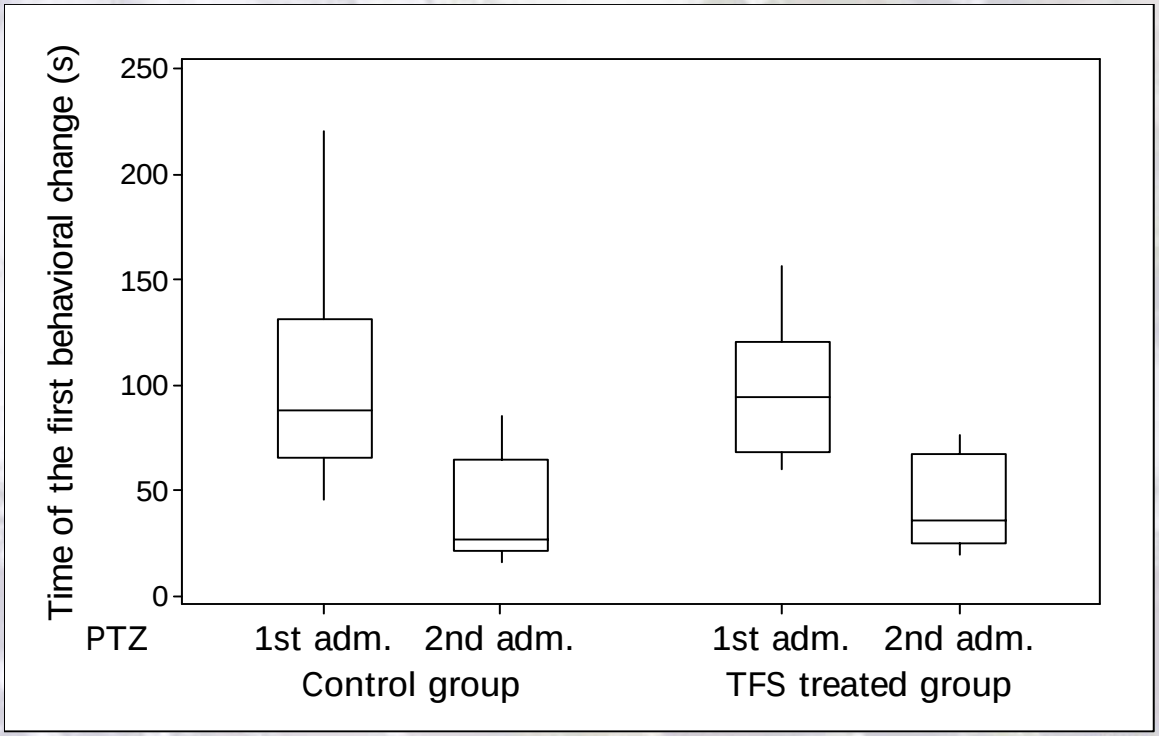
Behavioral activity

- This approach allows us to:
  - Compare the results from the first PTZ administration in the TFS-treated and control groups confirming that there is no significant difference between two groups (unpaired: two-sample Student's or Mann–Whitney);
  - Use the results for the first seizure as a baseline to study the difference between the first and the second PTZ-induced seizures in each group separately (paired: paired t-test or Wilcoxon signed-rank);
  - We compare the rates of change caused by recurrent PTZ administrations in control and TFS-treated groups to evaluate the effect of TFS.

- Time of the first behavioral change (not affected by TFS), seizure onset latency, duration of seizure, and maximal seizure severity score were studied TFS treated (n = 9) and control groups (n = 10):

Behavioral activity

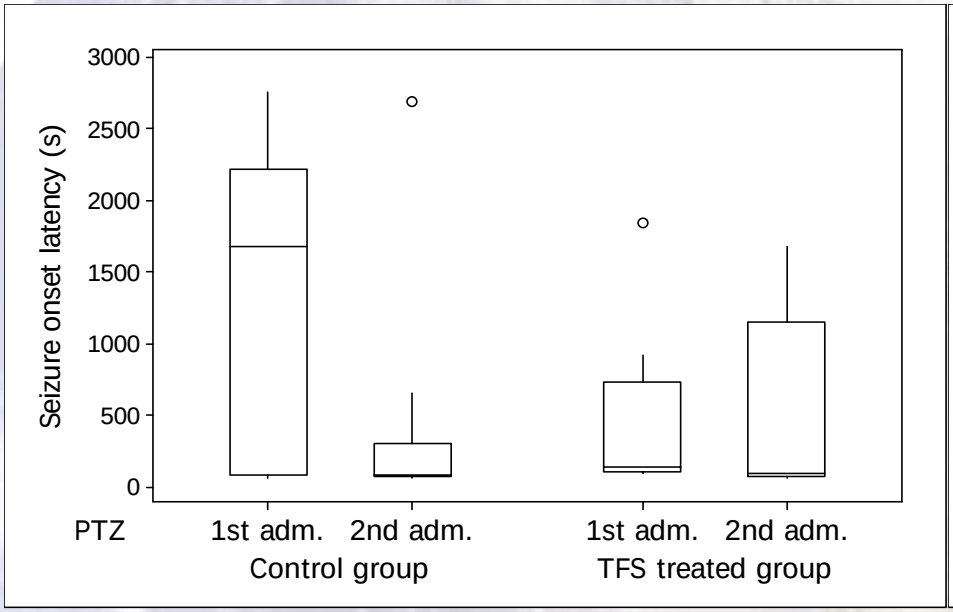
- Results: metric not affected by TFS

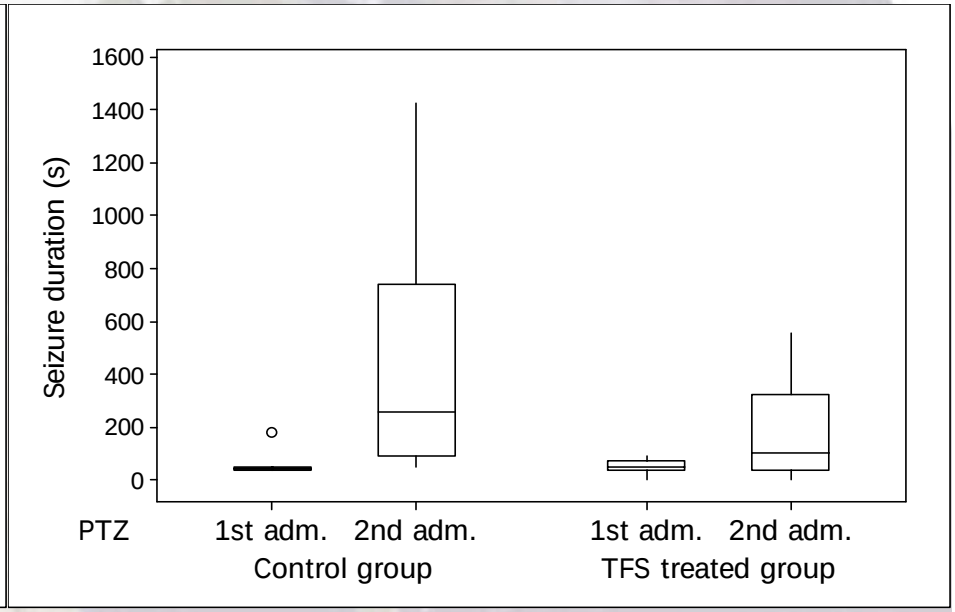


Makeyev et al. (2012a) *IEEE Trans. Neural Syst. Rehabil. Eng.* In press.

Behavioral activity

- Results: metrics affected by TFS





Makeyev et al. (2012a) *IEEE Trans. Neural Syst. Rehabil. Eng.* In press.

Behavioral activity

- Discussion:
  - There were no significant differences between two groups in any behavioral activity metric from the first PTZ treatment.
  - Time of the first behavioral change was significantly different between the first and second PTZ-induced seizures for both groups - TFS would not have any effect on it.
  - For other 3 metrics, while the general trend was the same, the difference was statistically significant in the control group but not in the TFS-treated group.
  - If this difference was due to some factor other than TFS all four metrics would have been likely to exhibit similar behavior.

Electrographic activity

- Assess the effect of TFS via TCRE on PTZ-induced electrographic seizure activity through comparison different stages of seizure development in TFS treated and control rats.

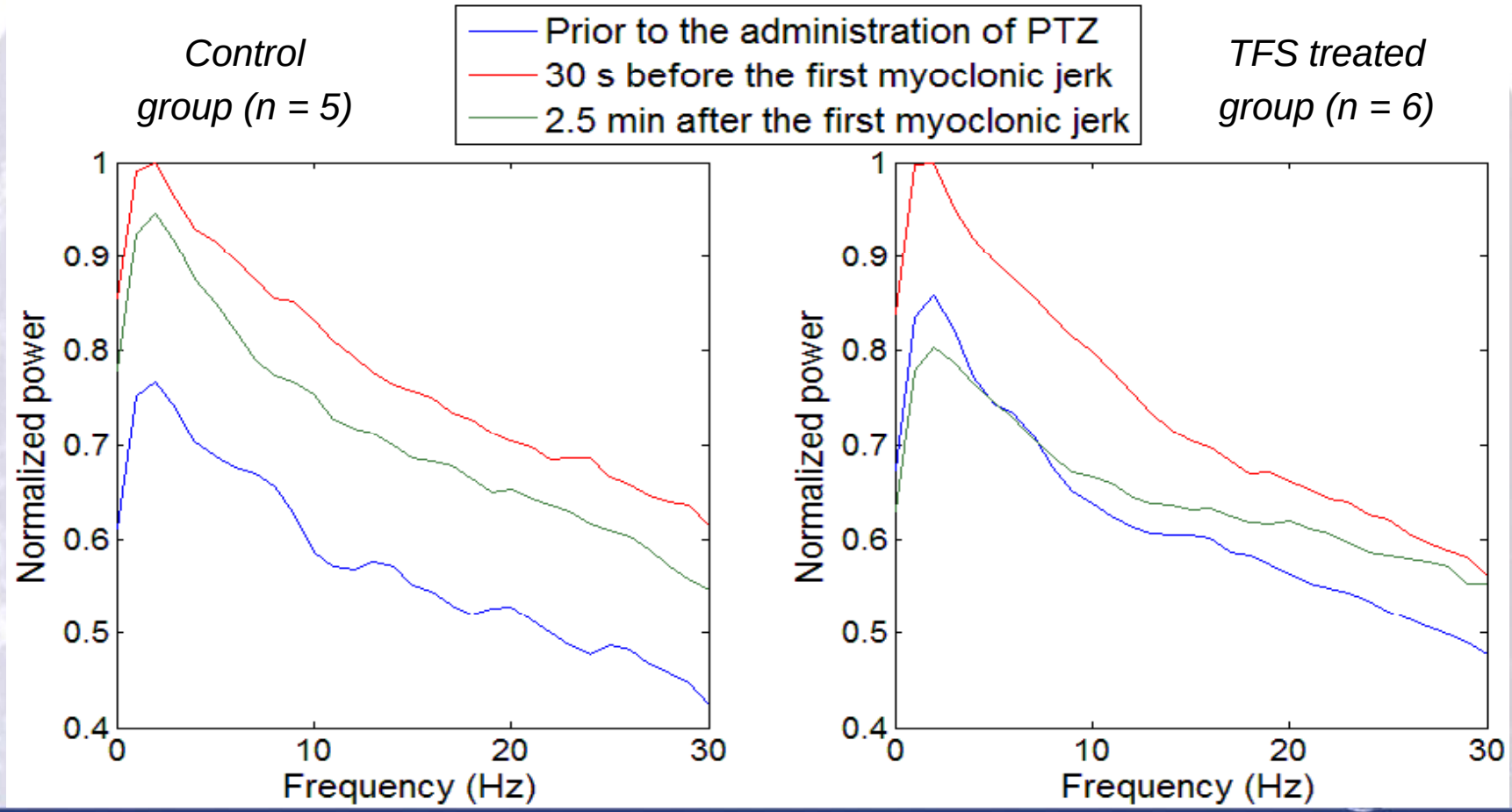
- Timeline:
  - The tEEG and the video recordings were started.
    - tEEG: EEG signals were preamplified (gain 100 and 0.3 Hz high pass filter), combined to give Laplacian derivation, amplified (gain 1000 and 1.0–100 Hz band pass and 60 Hz notch filtered), and digitized (16 bits, 256 Hz).
  - After five minutes of baseline tEEG recording the PTZ was administered (55 mg/kg, i.p.).
  - The TFS was manually triggered and administered immediately after the first MJ was observed [TFS treated group only].

Electrographic activity

- Methods:
  - Grand average power spectral density (PSD) estimates – comparing different stages of seizure development:
    - Three 30 s long segments were selected in the same way for each rat from control and TFS treated groups.
    - 1) Prior to PTZ administration – artifact free baseline; 2) 30 s before the first MJ – seizure activity; 3) 2.5 min after the first MJ – seizure activity.
    - PSD estimates were calculated using Welch's method and averaged.
  - Generalized likelihood ratio test (GLRT) – comparing average power of electrographic activity in two groups:
    - 4 min segments were selected starting 3 min after first MJ.
    - GLRT was applied to pairs of segments from control and TFS treated groups and the results were averaged for all the pairs.

Electrographic activity

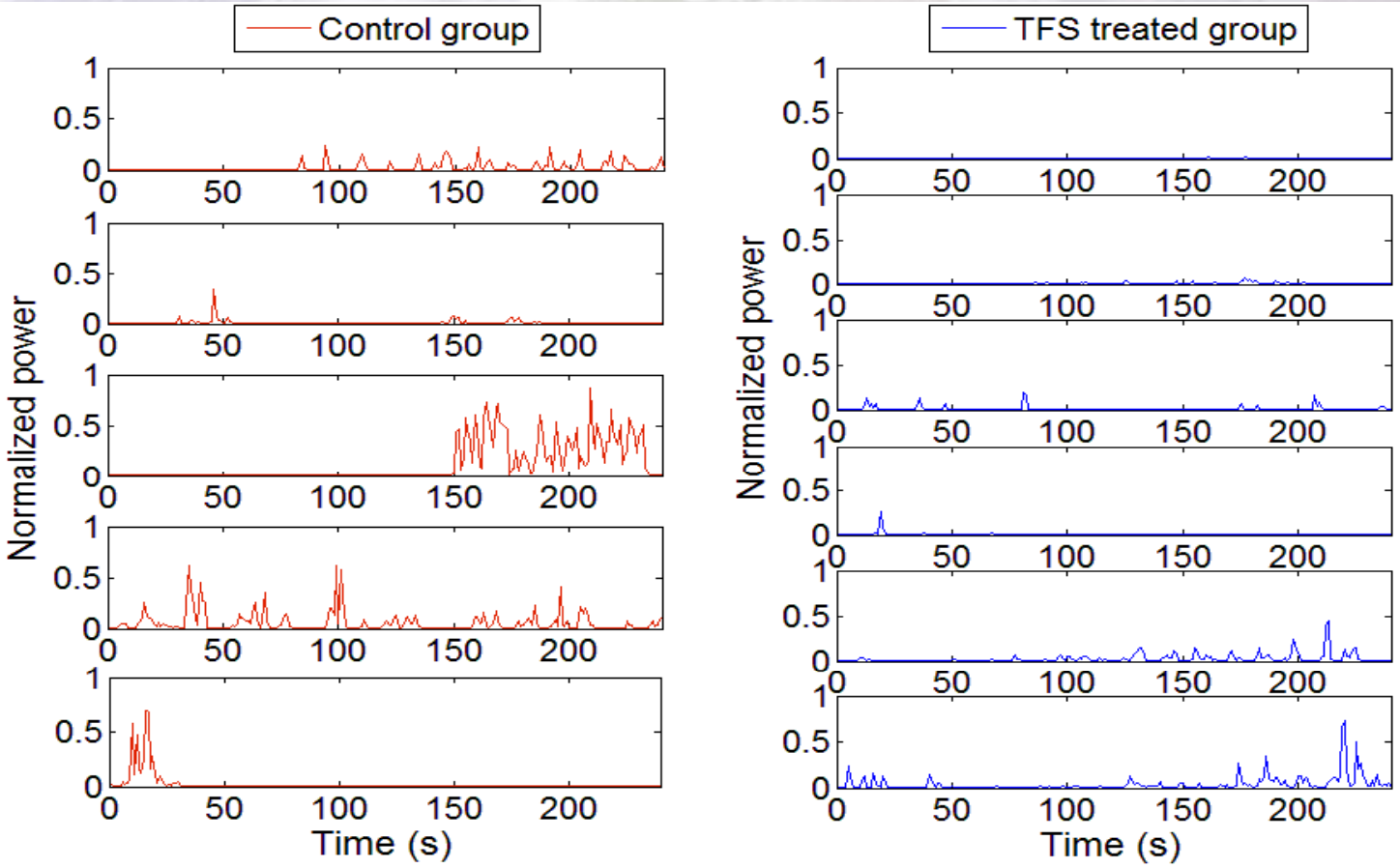
- Grand average PSD estimates:



Makeyev et al. (2011) *Proc. Conf. IEEE EMBS*, 7560-3.

Electrographic activity

- GLRT: Per second signal power



Makeyev et al. (2011) *Proc. Conf. IEEE EMBS*, 7560-3.

Electrographic activity

- Discussion:
  - Grand average PSD estimates show that after TFS power of the electrographic activity is reduced further towards the baseline in TFS treated group (1-15 Hz).
  - Current approach to segment selection:
    - Advantage: keeping it consistent for two groups for direct comparison;
    - Disadvantage: variability of seizure activity with intermittent intense spiking and absence.
  - GLRT was used for conclusive proof on larger segments: TFS significantly ($p<0.001$) reduced the power of electrographic seizure activity in the TFS treated group compared to controls in 80% of the pairs.
  - Why not base seizure onset detection on detecting the changes in signal power?

Closed-loop seizure control system

- Attempt to close the loop showing feasibility of an automatic seizure control system in rats with PTZ-induced seizures through single and multiple applications of TFS via TCRE.

- TFS is automatically triggered by real-time electrographic seizure activity detectors based on detecting the change in signal power.

- Confirm the effect of automatically triggered TFS on PTZ-induced electrographic seizure activity in rats (using the GLRT based approach from the previous section).

Closed-loop seizure control system

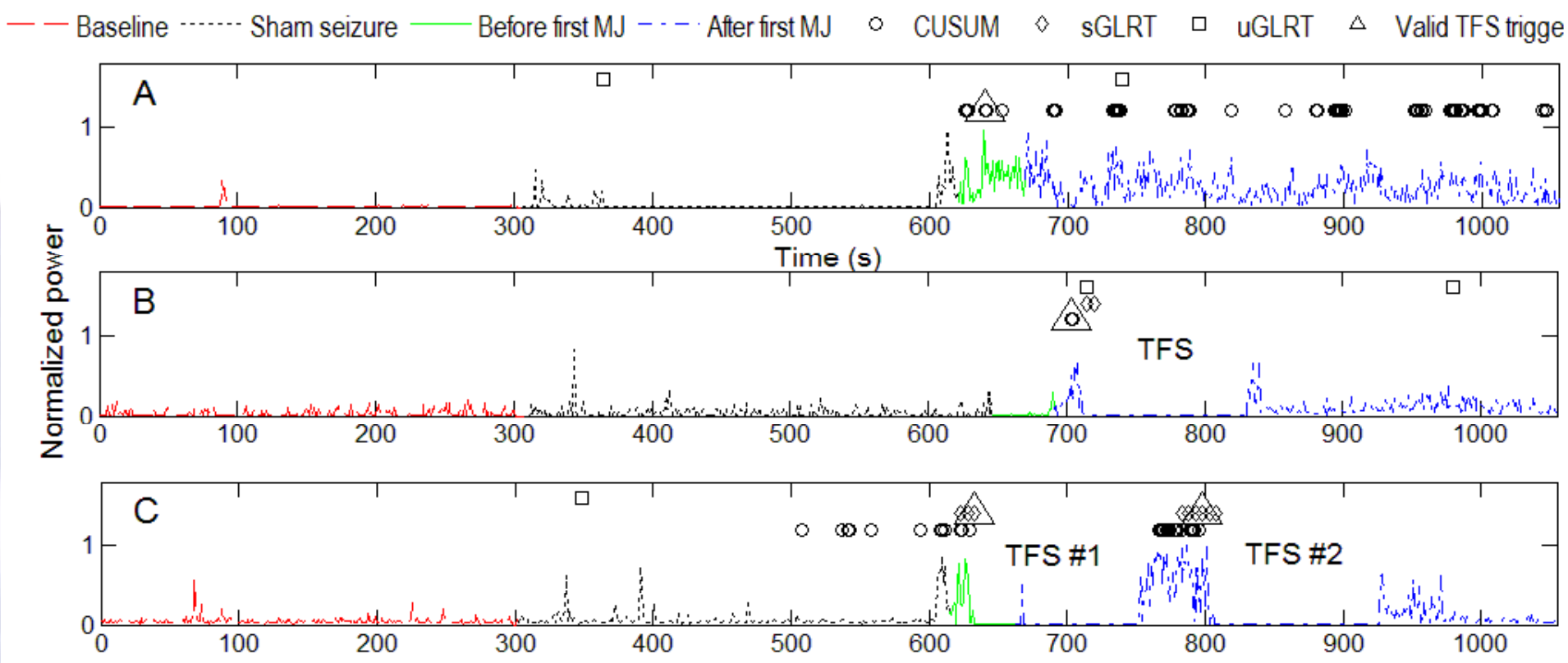
- Control group (n = 5) and two TFS treated groups: single dose (n = 5) and two doses (n = 3).

- We tested 3 seizure detectors (individualy and a disjunctive combination) including: cumulative sum algorithm (CUSUM) [1] and supervised and unsupervised implementations of GLRT (sGLRT and uGLRT respectively).

- Timeline:
  - 5 min of baseline tEEG were recorded to train the seizure detector;
  - The seizure detector was activated for 5 min of sham seizure activity (baseline);
  - Seizures were induced with PTZ (55 mg/kg i.p.) and the tEEG recording continued for another 15 min.

[1] Besio et al. (2011) *Proc. Conf. IEEE EMBS*, 5488-91.

Closed-loop seizure control system



Makeyev et al. (2012) *Epilepsy Curr.*, 12(s1): 29-30.
Makeyev et al. (2012b) *IEEE Trans. Neural Syst. Rehabil. Eng.* In press.

Closed-loop seizure control system

- Results:
  - For disjunctive (logical OR fusion) combination of three detectors:
    - An average seizure onset detection accuracy of 76.14% was obtained for the test set (n = 13) with median time from PTZ injection to detection equal to 18 s.
    - Detection of electrographic seizure activity was accomplished in advance of the early behavioral seizure activity in 76.92% of the cases.
  - TFS significantly (p = 0.001) reduced the electrographic seizure activity power in single dose group compared to controls in 70% of the cases.

Detector	Average accuracy (%)	Average sensitivity (%)	Average specificity (%)	Rats with seizure onset detected prior to the first MJ (%)	Median time from PTZ injection to detection of seizure onset (s)
CUSUM	74.47	23.06	91.9	61.54	56
sGLRT	78.31	21.47	97.66	61.54	46
uGLRT	75.32	1.22	98.72	23.08	118
Disjunctive combination	76.14	33.73	89.7	76.92	18

Makeyev et al. (2012) *Epilepsy Curr.*, 12(s1): 29-30.
Makeyev et al. (2012b) *IEEE Trans. Neural Syst. Rehabil. Eng.* In press.

Summary and future work

- Effect of TFS on behavioral and electrographic seizure activity suggests its anticonvulsant potential.
- To the best of our knowledge this is the first closed-loop automatic seizure control system based on noninvasive electrical brain stimulation using tEEG seizure activity as feedback.
- Future work on seizure detection:
  - Sensor integration of multiple TCREs (exponentially embedded family) [1];
  - Looking at power at higher frequencies (high-frequency oscillations) [2];
  - Moving to human data.

[1] Makeyev et al. (2012a) *Conf. IEEE EMBS*. Submitted.
[2] Makeyev et al. (2012b) Conf. *IEEE EMBS*. Submitted.

Acknowledgements

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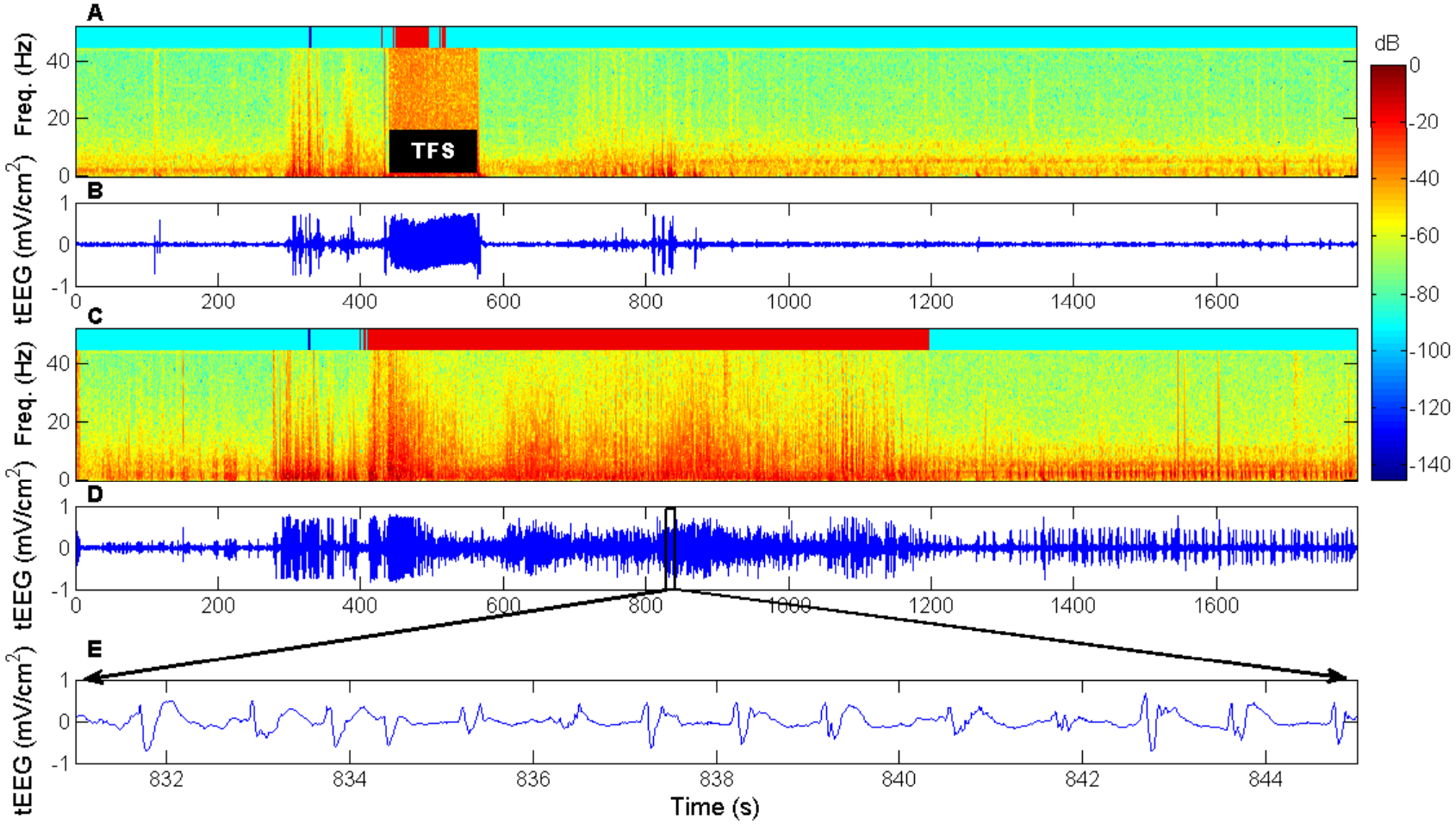
- Fall 2012, ELE 594: Applied statistical signal analysis for biomedical and electrical engineering applications
  - Cross-/autocorrelation;
  - Autoregressive and moving average models;
  - Linear prediction;
  - Power spectral density;
  - Fundamentals, advanced and application stages for each topic;
  - Utilizing data from you own research for applications and course project.

Tue, Thu: 6:15 - 7:30 pm, Bliss Hall 205

Thank you! Questions?

Combining behavioral and electrographic activity



Besio et al. (2012) *Epilepsia*. In revision.