

Non-invasive Suppression of Animal-model Chronic Epilepsy using Image-guided Focused Ultrasound

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Introduction: Non-invasive and controllable modulation of regional brain activity may open new avenues for various clinical applications ranging from functional brain mapping to treatment of numerous neurological and psychiatric disorders. MR-guided focused ultrasound (MRgFUS) technique allows for the non-invasive delivery of acoustic energy to a regional tissue, measuring few millimeters in diameter, depositing mechanical or thermal energy, which can be characterized by imaging modalities such as MRI. Utilizing the minimally-invasive nature of the FUS, selective modulation of regional neural activity in brain was sought after [Yoo et al. 2009], and we have further early results demonstrating the suppression of ictal activity in animal (rat) models of chronic epilepsy.

Method: Since the intra-peritoneal pentylenetetrazole (PTZ) injection induces rather non-focal epilepsy, direct intra-hippocampal injection of kainic acid (KA) was performed to create an animal chronic focal epilepsy (CFE) model to test the effectiveness of regional application of FUS for epilepsy suppression. Adult male SD rats (250-300g; n=4) were anesthetized and positioned in a stereotactic frame (SAS-4100, ASI Instruments, MI). After incision of the scalp, a burr hole was drilled on the skull to provide the entry point for the micro needle. 1µg KA dissolved in 1 µl normal saline was micro-injected unilaterally directly to the right hippocampus (5.6 mm posterior, 4 mm lateral, 6 mm ventral to the bregma). The animal was allowed to recover from the incision for 1 week prior to sonication, and we measured the behavior of the rats for 1 hour/day using the established Racine scoring system, once every two days. All animals developed recurrent spontaneous seizure activity (averaged Racine score = 3±0.8) 3-4 days after the injection. The severity and frequency of seizure was stabilized after one week (averaged Racine score = 1.5±0.8), which was consistent with the previous observations [Pace, 2002].

After one week of observation, the animals underwent MRI/EEG-guided sonication. With subdermal EEG electrodes (Ives EEG Solutions, Canada) administered for the detection of ictal activity, the animals received the sonication to the right hippocampus (the injection site) via stereotactic guidance of MRI (3Tesla, Spin Echo, 2" surface coil; T1-weighted 128×256 matrix; 8×8cm FOV; 64×64 image matrix; 3 mm slice thickness; no slice gap) and imaged most of the brain in the axial orientation. The EEG ictal signature, shown in Fig1. A-a, was characterized by stronger signal deflection (exceeding 200µV) and duration (more than 1sec), but low frequency (on the order of 2-4 incidents/min) compared to the PTZ cohort. Using the sonication parameters defined from the acute epilepsy model (690 KHz; TBD of 5msec and PRF of 100 Hz), sonication was administered at an AI of 50W/cm² for a duration of 1 min. Epileptiform activity was determined from the EEG activity and defined as discharges which lasted > 200msec and had a voltage amplitude at least 7 times greater than the pre-injection state.

FUS application in one animal immediately terminated all ictal activity after a single dose of sonication for the duration of the monitoring (15 min). For another animal, a single dose of FUS was not effective in suppressing the ictal activity, while 2 additional doses of sonication (noted as FUS2 and FUS3 in Fig. 1A) did suppress the ictal activity (Fig. 1A). The ictal activity data, assessed in 30 sec blocks, 1 min before, during, and 3 min after the sonication (n=4, Fig. 1B), suggested that sonication applied selectively to the lesion-site effectively suppressed the focal epileptic activity. We examined the temperature change of the sonicated tissue in order to evaluate (1) the potential tissue damage by heat and (2) the presence of temperature-related effects on the observed modulation of cortical excitability, by detecting changes in the water proton resonant frequency [Ishihara, 1995]. Changes in the resonant frequency were estimated using the phase images of a fast spoiled gradient echo (FSPGR) sequence (sequential multiphase, TE=14; FA=30; 256x128; 1 NEX, BW=17.9KHz), whereby we have not observed any tangible temperature elevation. The same doses of sonication were delivered to the hippocampus of control animals (n=2; without epilepsy-induction), which then underwent histological screening (H&Es stains). There was no damage to the tissue or surrounding vasculature in the sonicated site.

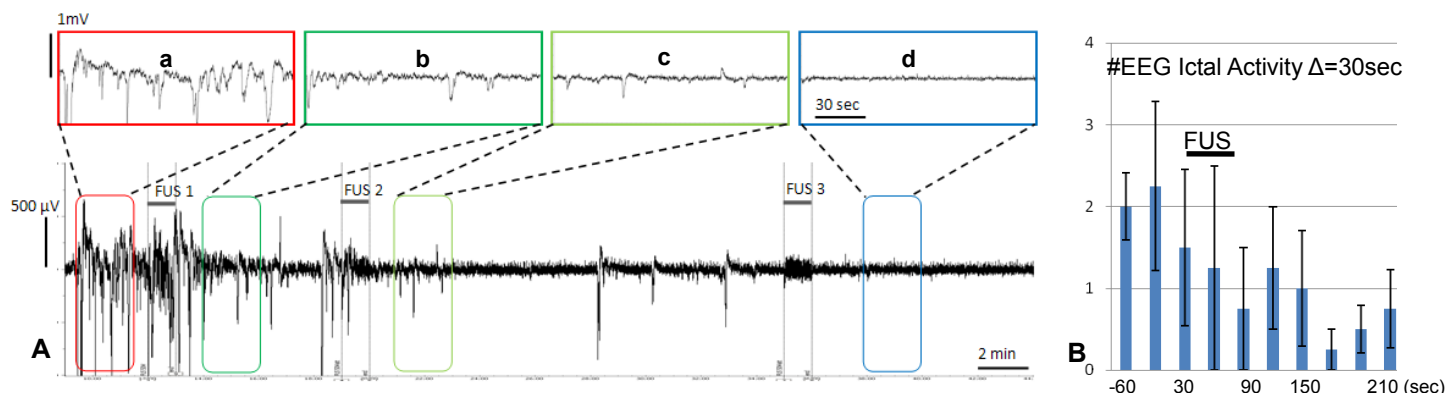


Fig. 1 (A) The lower plot shows the time course of the sample EEG from a rat with KA-induced CFE. The ictal activity during pre-sonication (block-a) started to diminish during the multiple sessions of sonication (marked with a gray-lines; FUS 1~3) and effectively suppressed after the end of sonication (block-d). (B) The changes in occurrences of ictal activity counted every 30-sec block before, during, and after the sonication.

Discussion: Our preliminary data show that (1) selective suppression of CFE is possible via non-invasive FUS application, and (2) multiple sessions of sonications are needed for complete extinction of the ictal activity. Remaining goals are to (1) confirm the findings with more animals, and (2) to assess the presence of long-lasting suppressive effects and their relation to multiple doses of sonication. Furthermore, comprehensive data describing the biological effects supported by behavioral and electrophysiological monitoring are urgently needed to address the safety and effectiveness of the procedure.

Reference: [1] Yoo, ISMRM (2009), proceedings, #1795. [2] Ishihara, Magn Reson Med 1995; 34: 814-23. [3] Pace, J Neurosurg. 2002; 97(2):450-4.