Delivery of Low-Intensity Pulsed Ultrasound in the Cortex to Improve Longevity and Performance of Neural Interfaces

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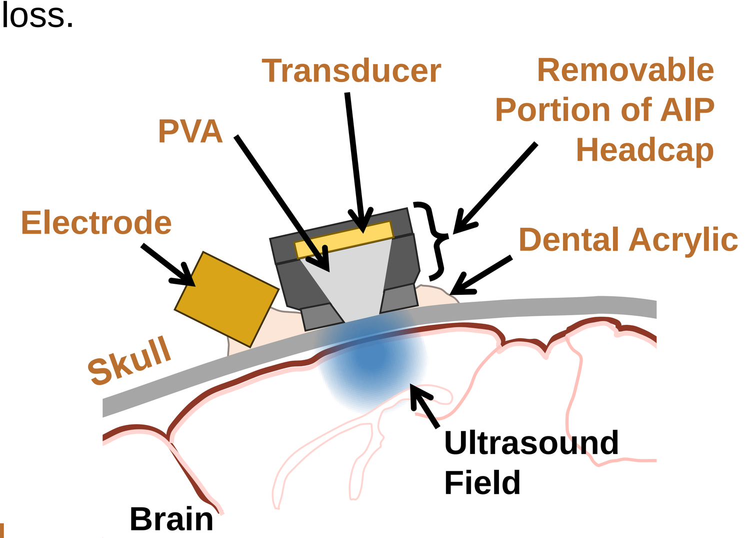
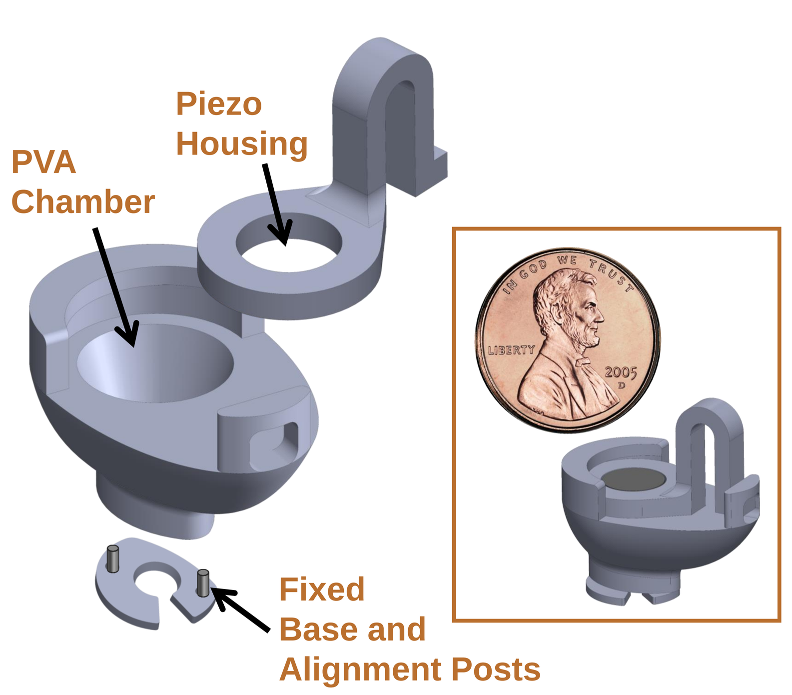
Introduction

+ Chronic neural implants hold great potential for illuminating features of neural function, treating neurological disorders, and enabling the next generation of neuroprosthetics.
+ Penetrating electrode arrays provide direct access to neural signals.
+ Points of failure for chronically implanted microelectrode arrays:
  - Poor longevity and variability in functionality.
  - Foreign body response (FBR) can cause glial scarring and neural cell loss near electrode sites.
  - FBR begins with electrode insertion
  - FBR mitigation efforts:
    - Limiting insertion damage during implantation,
    - Reducing the mechanical mismatch between brain and implant, and
    - Suppressing FBR by incorporating exogenous chemicals.
+ This study investigates the use of sub-threshold **low-intensity pulsed ultrasound (LIPUS)** to improve tissue health at the neural interface.
  - LIPUS has been shown to have protective and healing effects in models of cerebral disease and injury, through promotion of brain-derived neurotrophic factor and other neurotrophic factors.
+ Our work demonstrates that periodic application of localized LIPUS to tissue at the neural interface can promote:
  - Improved electrophysiology signal quality, as measured via signal-to-noise ratios, electrode single-unit yields, and histological evaluation of glial scarring.

Acoustic implant protection (AIP) using low-intensity pulsed ultrasound

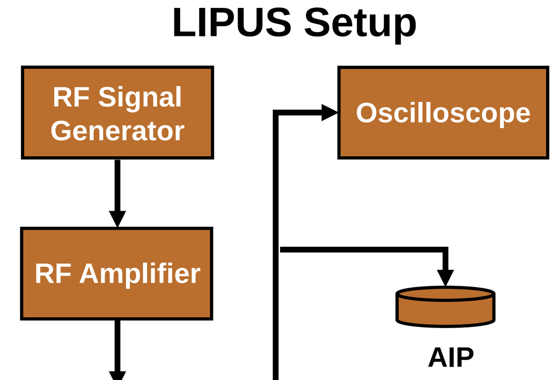
+ Transducer assembly designed for integration with an angularly inserted neural electrode. The base component is fixed to the skull over targeted stimulation region for transducer alignment. The transducer and acoustic horn are affixed only during stimulation.
+ Ultrasound transducer mechanically coupled to skull by biocompatible polyvinyl alcohol (PVA) acoustic horn. PVA can be acoustic impedance-matched to skull to minimize acoustic energy loss.
+ Brain activity of LIPUS-stimulated (n=4) and Control (Sham, n=4) Subjects recorded with neural electrodes over 6-week test period.



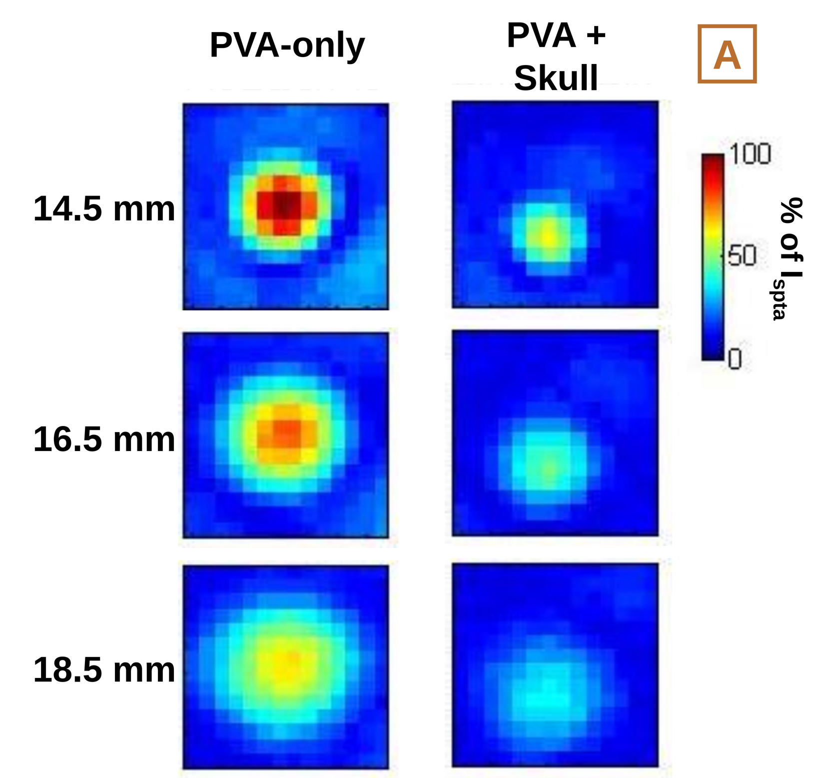


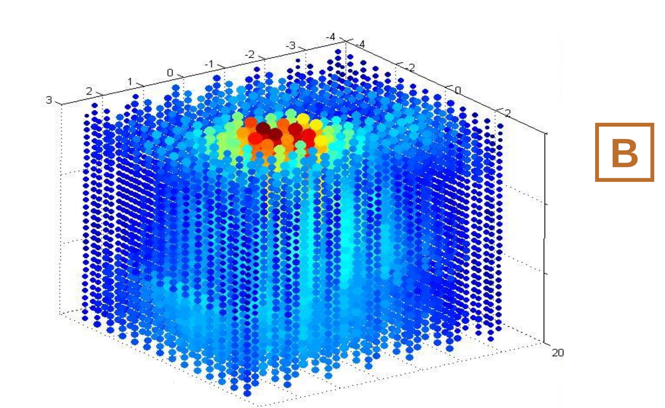
The 3D printed Headcap incorporated a fixed portion for alignment and releasable portion capable of removal between treatments. The releasable portion included a clip-cap for addition of the PVA horn between the piezo ultrasound source and skull surface for acoustic coupling.

Schematic Diagram of LIPUS Setup



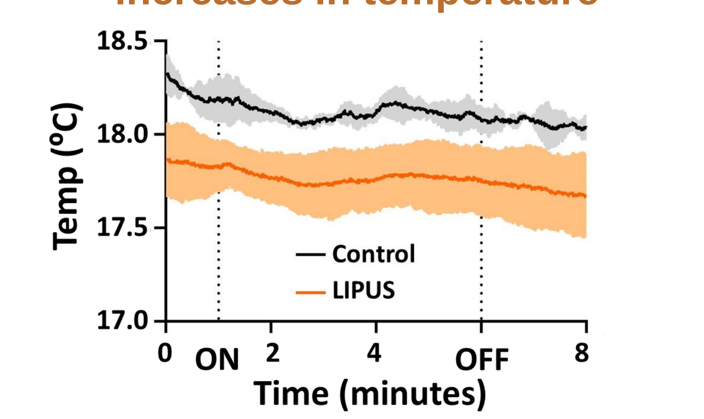
Ultrasound maintains focus following transmission through the skull





Temporal average acoustic intensity from each piezoelectric transducer measured throughout a 7 x 7 x 15 mm volume in water at a spatial resolution of 1 mm. **A.** Ultrasound energy as a ratio of peak energy at different distances from the piezoelectric transducer as measured in water through PVA horn with and without ex vivo rat skull. **B.** Measurements acquired with a voxel size of 0.5 x 0.5 x 0.5 mm³. **Average transmission of the ultrasound through the skull was 49% of peak intensity of ultrasound in water.**

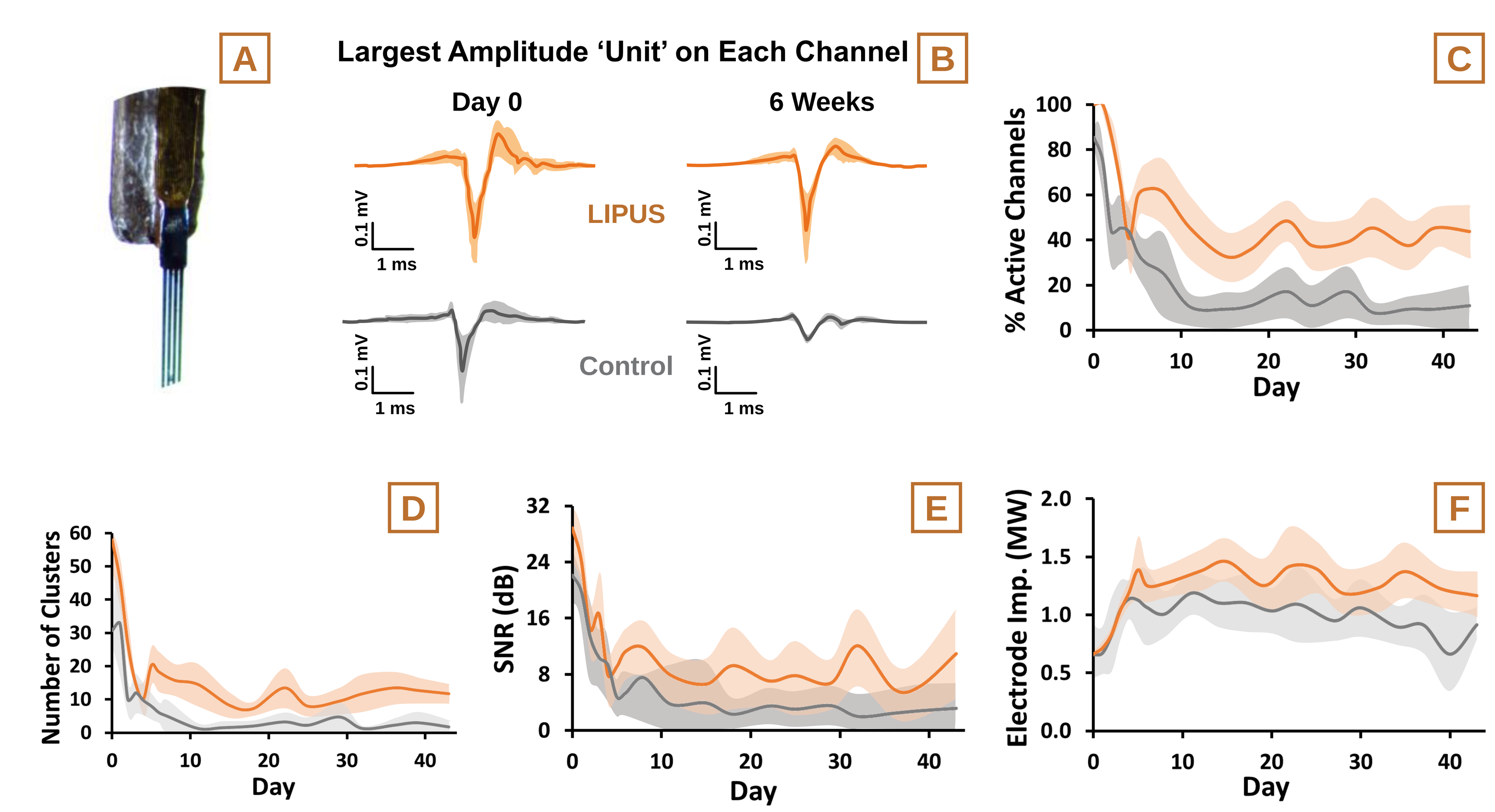
Ultrasound does not induce increases in temperature



Thermal analysis during exposimetry testing over a 5-minute operation (5% duty cycle) as measured with thermocouples. No significant heating effects were observed. Curves depict Mean ± Mean Std. Err.

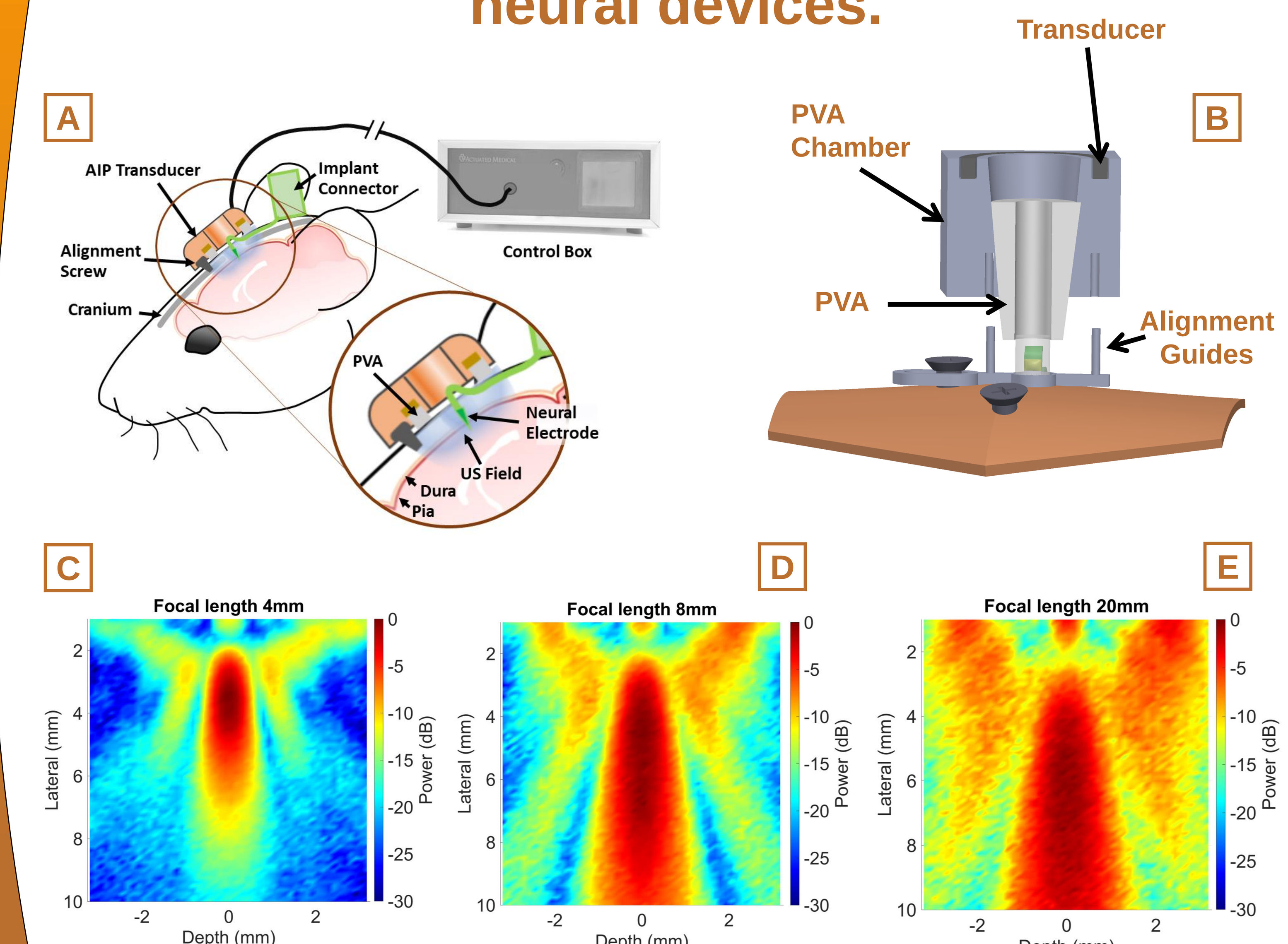
LIPUS improves signal patency in chronic in vivo studies

+ Sprague-Dawley rats (Male, N=8; 180-200 g).
+ 4-shank silicon NeuroNexus arrays (A4x4-5mm-100-125-703-CM16LP) inserted into cortical layers II/III of the motor or somatosensory cortex to 1.2 mm depth and at an angle of 45º.
+ Average unit waveforms recorded pre-stimulation (1.1 MHz, 0.5 W/cm², 3x5 min treatments at 4% duty cycle (2 Hz repetition)) at each session; daily treatments performed in Week 1, followed by twice weekly treatments during Weeks 2-6.



A. NeuroNexus A4x4 16-channel probes implanted at 45°angle relative to cortical surface to record neural activity **B.** LIPUS treated subjects maintained larger amplitude spikes over duration of 6-wk recording period. **C.** Percent of active channels and number of clusters (post-curation) over 6-wk post surgery period for LIPUS and Control (Sham) cohorts (n=4/treatment). After 1-wk, the average percent (%) of active channels (p<0.01) and **D.** Number of measured clusters (p<0.01) were observed to be greater in the LIPUS-treated cohort. Curves depict Mean ± Mean Std. Err. **E.** Signal-to-noise ratio (SNR) of remaining active channels and **F.** Electrode impedance over 6-wk post surgery period for LIPUS and Control (Sham) cohorts (n=4/treatment) over 2-6 wks, the average SNR of the active channels was nearly 5 dB higher in LIPUS treated (p=0.386) cohort despite an increased electrode impedance. Curves depict Mean ± Mean Std. Err. Orange = LIPUS, Gray= Control (Sham). Statistical Analysis= Student's t-test at 6 wks.

Development of annular transducer for effective ultrasound stimulation around neural devices.



A. Many chronically implanted devices are implanted perpendicular to the skull surface potentially interfering with acoustic fields directed towards electrode shanks **B.** Prototype design of conical ultrasound transducer, horn and skull plate used to direct acoustic fields around superficial aspect of neural devices. **C.-E.** Simulation of acoustic field intensity of an annular ultrasound transducer using the Field II ultrasound modeling package in MATLAB. Element dimensions (OD: 6.5 mm, ID: 2.5 mm,, Frequency: 1.2 MHz) Manipulation of transducer face curvature provides ability to shift peak ultrasound intensity field to target superficial or deep brain regions. Increasing focal depth expands field of peak intensity in xy and yz planes altering volume of tissue receiving stimulation **C.** Focal length: 4 mm, **D.** Focal length: 8 mm, **E.** Focal length 20 mm.

Summary & Future Direction

+ LIPUS application improves longer-term neural electrode viability.
  - Given the minimal change in electrode impedance, the mode of action is under investigation.
  + Sub-threshold LIPUS supplication appears to be safe over several-week treatments, though follow-up studies are warranted.
  + Future development is focused on optimizing ultrasound field steering to electrode shanks of vertically implanted and large form-factor neural devices.

References & Acknowledgements

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