

Focused Ultrasound Neuromodulation of the Sciatic Nerve for Inflammatory Pain Reduction in Mice

Background, Motivation and Objective

Chronic pain affects 20% of adults, with current treatment relying on prescription medications with varying efficacy and potential for abuse. Peripheral focused ultrasound (FUS) can modulate neural activity, with studies demonstrating pain reduction in healthy and chronic pain subjects. The most effective FUS parameters for pain reduction, the duration of this alleviation, and its efficacy compared to pharmaceuticals are unknown, however. This study evaluated the optimal parameters for FUS-induced inflammatory pain reduction in mice over a 15 day period and compared the results to drug induced pain relief.

Statement of Contribution/Methods

Twenty-four (n = 24, 50:50 female:male) mice were used across four cohorts (positive control, negative control, FUS treated, drug treated) over a 15 day period (**Fig 1a**). Inflammatory pain was induced on day 0 via right footpad injection of 30 μ L complete Freund's adjuvant (CFA) (n = 18). 30 μ L saline was injected for negative control mice (n = 6). Pain was measured via von Frey withdrawal thresholds and motor performance via rotarod and CatWalk. On day 2, the sciatic nerve in the right leg was located with B-mode imaging and sonicated in the FUS cohort (n = 6) (**Fig 1b**). Targeting was confirmed with a 1 ms, 28 MPa pulse to induce leg movement and nerve displacement imaging. The treatment parameters (3.1 MHz, 1 ms pulse duration, 10 Hz PRF, 60 s sonication duration, 10.1 MPa peak-positive pressure, 5 sonications with 1 minute period) were found via a parameter exploration study on separate female mice (n = 11) (**Fig 1c**). The drug cohort received subcutaneous injections of ibuprofen (100 mg/kg) 45 minutes before behavior testing on day 3 (n = 6).

Results/Discussion

Pain, as measured by withdrawal threshold reductions in the injected foot compared to the control foot ($p < 0.0001$) (**Fig 1d**), and edema ($p < 0.0001$) (**Fig 1f**) were successfully induced in all CFA mice by day 1. FUS treated and drug treated mice had significantly greater thresholds on day 3 compared to the positive control ($p < 0.0001$), indicating analgesia in both treatment groups. FUS showed continued withdrawal improvement on day 7 compared to the positive control ($p = 0.0064$). Rotarod (**Fig 1f**) and CatWalk (**Fig 1g**) data demonstrate that FUS did not impair motor function. These results indicate the potential for FUS-induced inflammatory pain reduction with effects lasting up to 5 days post-sonication.

