Ultrasound-Mediated Blood–Brain Barrier Permeabilization Enables Targeted Drug Delivery in a Murine Model of Neuropsychiatric SLE (NPLSE)

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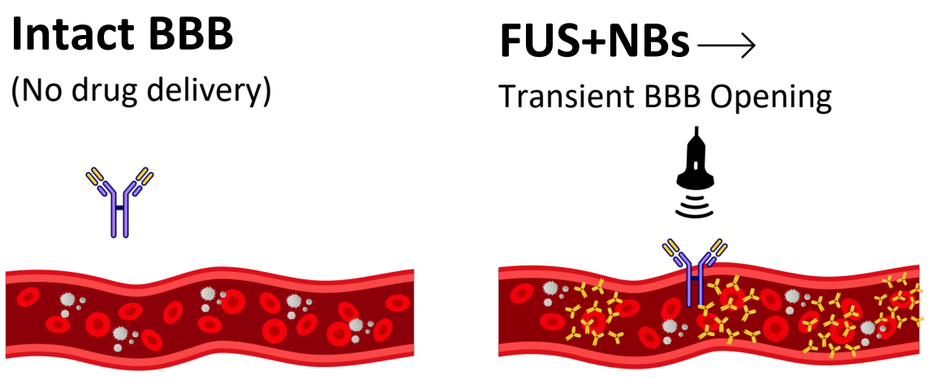
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Introduction

Neuropsychiatric SLE (NPSLE) is a severe complication of lupus involving the CNS, and leading to cognitive, behavioral, and neurological deficits.

Therapeutic monoclonal antibodies (mAbs) show promise in SLE but are limited in NPSLE due to the restrictive blood–brain barrier (BBB).

We explored focused ultrasound (FUS) with nanobubbles (NB) as a non-invasive approach to transiently open the BBB and enhance CNS delivery of therapeutic antibodies.

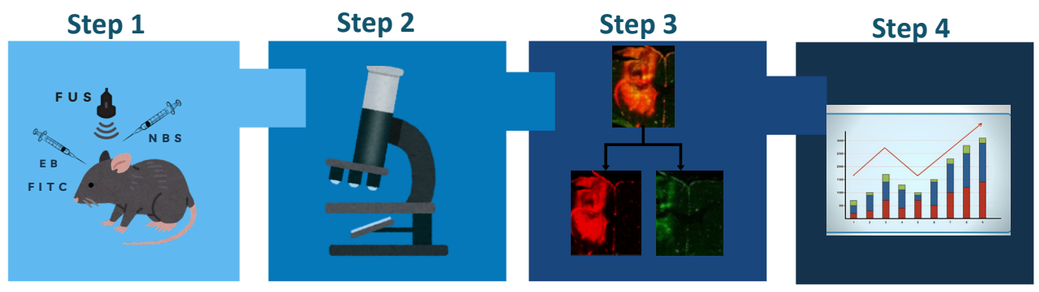


Methodology

Twelve-week-oldfemale MRL/lpr mice (NPSLE model) were studied. Two experiments were performed:

Experiment 1: Two 10 week-old Female B6 mice received nanobubbles (NB, 180 nm) via retro-orbital injection followed by unilateral focused ultrasound (FUS, 850 kHz, 210 kPa, 1 min). Evans Blue (EB) was injected and brains analyzed by ELISA to measure the concentration of EB as an indication of BBB permeability.

Experiment 2: *Six lupus-prone MRL/lpr and six MRL/mpj control mice underwent the same NB-FUS protocol. Following FUS, Evans Blue (EB) and FITC-dextran (150 kDa) were administered. In addition, another experiment was performed using the same protocol, but without dextran injection, and the treatment was bilateral. Brains were harvested for fluorescence microscopy to assess tracer uptake and distribution.*



Results

Quantitative analysis showed significantly higher Evans Blue (EB) concentrations in NB-FUS–treated hemispheres compared with the contralateral side (normalized values: **1** treated right hemispheres (R: 0.353, 2R: 0.239 vs. **1** untreated left hemispheres: 0.199, 2L: 0.194; Fig. 1), confirming spatially targeted BBB disruption.

- ***In the second experiment***, EB penetration was macroscopically visible in the ultrasound-targeted hemisphere of 8/12 mice. Fluorescence microscopy showed EB and FITC-dextran uptake in the treated hemisphere with minimal contralateral signal (Fig. 2). In bilaterally treated mice, EB was evident in both hemispheres, extending across the targeted brain regions. No major differences were observed between lupus-prone and control strains. Ongoing experiments are testing CNS delivery of a labeled therapeutic antibody in the same model.

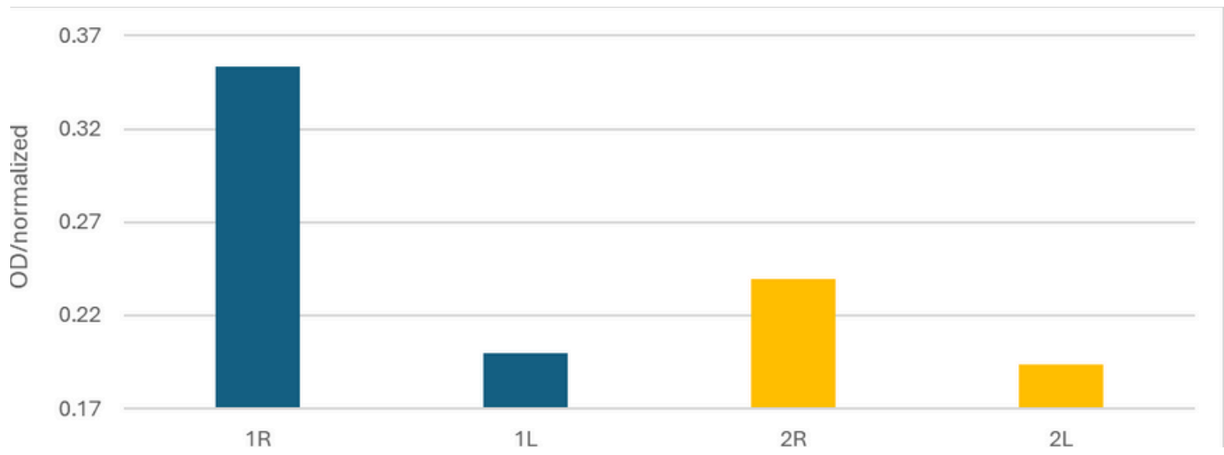


Figure 1. Brain EB concentration. Optical density reading comparison between the FUS-treated right hemispheres (R) and the untreated left hemispheres (L) within individual mice.

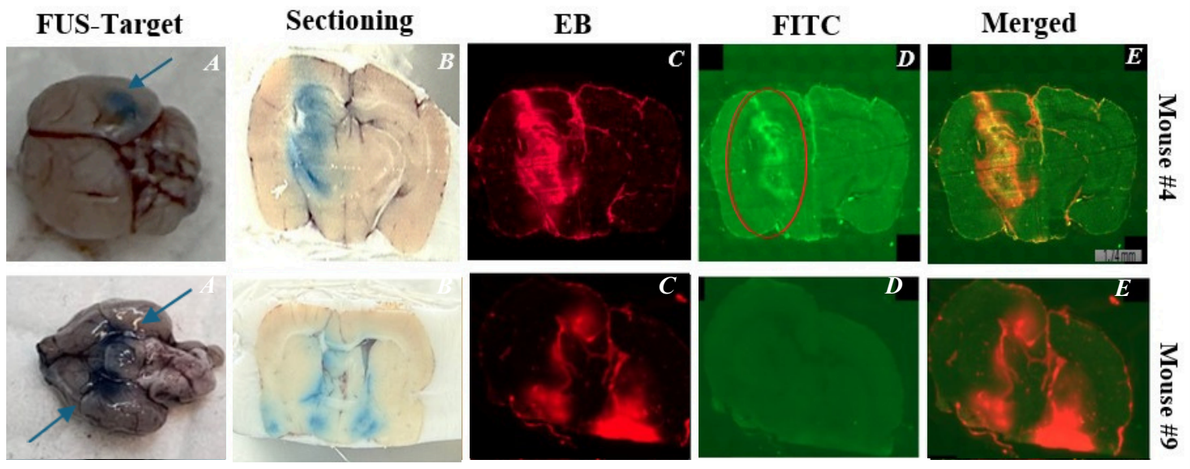


Figure 2: Focal ultrasound application following nanobubble administration locally permeabilizes the BBB nd enables delivery of an antibody-sized molecule into the CNS. **A**. Representative image of mouse brains immediately after ultrasound treatment, showing localized blue staining indicative of EB penetration into the brain parenchyma. **B**. A brain section during cryostat slicing, demonstrating widespread EB presence throughout the targeted ultrasound-treated region. **C**. Magnified (4×) image of the brain highlighting EB distribution in red fluorescence within the treated area. **D**. Magnified (4×) image showing FITC fluorescence in green (circled in red), indicating distribution of this additional tracer within the treated brain region. **E**. Merged image of C and D combining EB (red) and FITC (green) signals, demonstrating both tracers' penetration and co-localization within the ultrasound-targeted area.

Conclusion

- FUS + NB safely and effectively enhanced BBB permeability in a murine NPSLE model.
- This study demonstrates the feasibility of targeted CNS delivery of therapeutic antibodies.
- Our approach highlights the potential for treating autoimmune neuroinflammatory diseases such as NPSLE.