Effect of Aging and Biological Sex on the Acoustical Properties of Murine Skulls

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Opening the blood-brain barrier (BBB) using focused ultrasound (FUS) and peripherally-administered microbubbles, via acoustic cavitation, is a promising technique for targeted drug delivery to treat neurodegenerative disorders, such as Parkinson's Disease and Alzheimer's Disease. To reach the intended target in the brain, the FUS beam must pass through the skull, a structure which causes varying beam distortions due to its complex structural properties. To achieve consistent therapeutic effects across subjects, the effects of age and biological sex on these properties should be understood and corrected for. Excised murine skulls, varying in age, strain, and biological sex, were degassed for over 24 hours before beginning attenuation experiments to ensure proper acoustic coupling. The center of the acoustic focus of a 1.5 MHz FUS transducer was first localized in a custom-made water bath using a needle hydrophone to perform raster scans of the acoustic field in the axial and circumferential dimensions. Free field measurements were taken prior to skull placement in the path of the ultrasound beam and acquisition of insertion loss ($Insertion\ Loss = \frac{Regional\ Pressure}{Free\ Field\ Pressure} * 100$) measurements in the left and right frontal and parietal regions. A statistically significant difference between the average insertion loss for male and female mice was observed (Fig.1A). No statistically significant differences in average insertion loss between the three defined age groups (young mice 0-6 months old, middle-aged mice 7 months-1.7 years old, and old-aged mice 1.8-2.3 years old) were found, however, a globally linearly increasing trend (R^2=0.6804) was observed (Fig.1B). For female mice, a significant increase in average insertion loss between the age groups was found, exhibiting a strong linear correlation (R^2=0.9942). A small, albeit statistically insignificant, increase in average insertion loss was detected among male mice across the age groups, with a strong linear correlation (R^2=0.9771), (Fig.1-C). Though there were many limitations to this study, a main one being the difficulty in accounting for variability in skull structure, aging in female mice was shown to lead to a significant increase in insertion loss. Further work can be conducted using micro-CT analysis to quantify the changes in the microstructure of the skulls, specifically the thickness and porosity, which may explain insertion loss results.

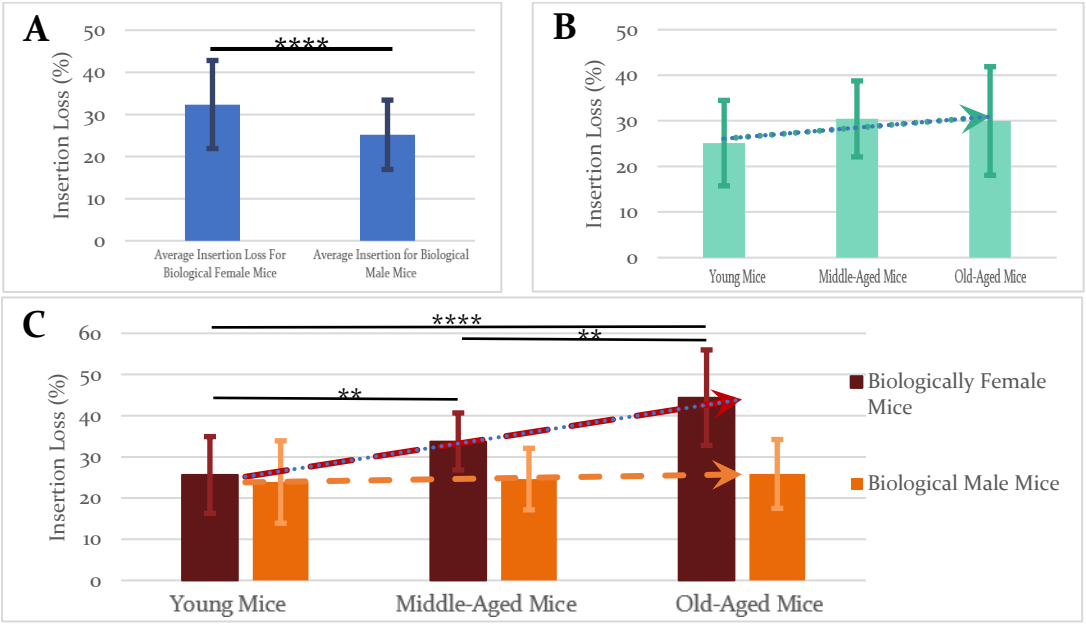

Figure 1: A) Average insertion loss of biological female mice statistically greater than that of biological males, ****p < 0.0001 determined by Student's t-test (n =13-14) **B)** One-way ANOVA test showed no statistically significant differences between age groups (trendline y=2.43x+23.6, R^2=0.6804) **C)** Statistically significant differences between age groups in the biological female population were confirmed by a two-way ANOVA, followed by a post-hoc Tukey's multiple comparison test (red trendline y=9.39x+15.8, R^2=0.9942), **p<0.01 (n=8-28). No statistically significant differences between the age groups in the biological male population (orange trendline y=0.98x+22.8 R^2=0.9771)

Acknowledgements: National Institutes of Health (R01AG038961 and R01EB009041)
Focused Ultrasound Foundation
Columbia University and Amazon Summer Undergraduate Experience Program