Transcranial Theranostic Ultrasound Pre-Planning and Blood-Brain Barrier Opening
Using a Phased Array In Vitro and In Vivo

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This study utilizes in vitro and in vivo theranostic ultrasound (TUS) treatment pre-planning to inform transcranial blood-brain barrier opening (BBBO) in mice with overlaid primate skull fragments using a single phased array.

In vitro experiments were conducted using a hydrophone (Fig. 1A) and microbubble flow channel (254 µm diameter, 8.0E8 microbubbles/mL) (Fig. 1B) to determine the expected transcranial pressure loss and focal shift induced by the skull, respectively. Simulations were conducted using the k-wave MATLAB toolbox with micro-CT scans (0.08 mm resolution) of primate skull fragments to evaluate steering angle-dependent attenuation and focal shift of the TUS beam. Synchronous in vivo transcranial BBBO and power cavitation imaging (PCI) was performed using the P4-1 phased array (1.5 MHz, 450 kPa derated peak-negative pressure, 35 mm focal depth, ±3.72 degree electronic steering angle), operated by a Verasonics ultrasound system (Vantage) (Fig.1C) in mice (C57BL/6J).

Simulations revealed significantly increased attenuation and axial focal shift magnitude with larger steering angle magnitudes through the non-human primate (NHP) skull (Fig.1D-E); no significant differences were observed through the human skull (Fig.1F-G). In vitro skull experiments demonstrated 0.3-1.5 mm axial and lateral focal shifts induced by the skull as confirmed by comparison between contrast-enhanced B-mode and PCI images acquired in the channel phantom. In vivo transcranial BBBO was achieved bilaterally, exhibiting high correlation between regions of contrast-enhancement on T1-weighted MRI and -6 dB regions in corresponding PCI (Fig.1H-M).

Feasibility for synchronous transcranial BBBO and PCI using a single theranostic phased array was demonstrated in mice in vivo.
Figure 1: Experimental setup for (A) transcranial attenuation measurements, (B) *in vitro* cavitation mapping registration error calculations, and (C) *in vivo* transcranial BBB opening. Simulated steering angle dependent focal shift and attenuation through NHP skull fragment (D-E) and human skull fragment (F-G). Statistical significance determined by a one-way ANOVA with post-hoc Tukey’s multiple comparisons test where, **p<0.01, ***p<0.001, ****p<0.0001, for n=6 simulation trials. Region of contrast enhancement on T1-weighted MRI and corresponding cavitation map for BBB opening through the NHP skull (H-I) and human skull (J-K). Area under the receiver operator characteristic (ROC) curve depicting correlation between gadolinium diffusion maps and cavitation maps through (L) NHP skull and (M) human skull (n=4 mice per group). All error bars denote the mean ± standard deviation.