Targeting Effects on the Volume and Gray-To-White-Matter Ratio of the Focused-Ultrasound Induced Blood-Brain Barrier Opening in Non-Human Primates In Vivo

Maria Eleni Karakatsani[1], Gesthimani Samiotaki[1], Matthew Downs[1], Vincent Ferrera[2], and Elisa Konofagou[1,3]

[1]*Department of Biomedical Engineering, Columbia University, New York, NY, United States,* [2]*Department of Neuroscience, Columbia University, New York, NY, United States,* [3]*Department of Radiology, Columbia University, New York, NY, United States*

Purpose:

Focused Ultrasound (FUS) has been shown capable of allowing drug diffusion into the brain parenchyma for the treatment of Central Nervous System (CNS) disease. The application of FUS coupled with the systemic administration of microbubbles has been proved to open the Blood-Brain Barrier (BBB) locally, transiently and non-invasively in non-human primates (NHP). In this study, the targeting accuracy of the induced opening ($\boldsymbol{V_{BBB}}$) and the associated safety of the method are determined using MRI. The inhomogeneity of the NHP brain presents an important challenge when assessing the dependence the volume of the induced opening ($\boldsymbol{V_{BBB}}$) has on the targeting parameters and the underlying structure of the brain region targeted. One of the objectives of the study is to determine the relationship between the V_{BBB}, the FUS pressure and the incidence angle for more accurate outcome predictions in treatment planning. A secondary objective entails the shift in the geometric focus due to the skull aberrations and dependence on the gray-to-white-matter ratio in the brain region targeted.

Methods:

Five (n=5) NHP, i.e., four mulatta and one fascicularis macaque, were sonicated in the caudate (Cau) and putamen (Pu) using FUS (F_O: 500kHz; PRF: 2Hz; duration 120s; PNP 275-600 kPa) while being intravenously administered with monodisperse (4-5 micron in diameter), lipid-coated, gas-filled microbubbles. The NHPs were scanned in a 3T MR system (Intera, Philips) acquiring 3D T1 weighted (T1w) pre- and post-contrast images (FFE: TR/TE=8.6/4.8 ms; FA=8°; res 1x1x1mm^3) 30 min and approximately 24 hours after BBB opening to allow for visualization of the induced opening. T2 weighted (TR/TE=3000/80 ms; FA=90°; res 1x1x2 mm^3) and SWI (TR/TE=19/27 ms; FA=15°; res 1x1x1 mm^3) images were also obtained to determine the safety of the method. The estimation of the incidence angle and the center of the targeted region were established by projecting the ultrasound beam propagation and the focal region onto the BBB opening site detected on post-contrast T1w images. To quantify the shift, an automated intensity-based algorithm was designed that identified the centroid of the targeted region and the V_{BBB}. Finally, the opening was overlaid onto the brain region on a segmented T1w image to quantify the percentage of gray matter (GM) and white matter (WM) with opened BBB.

Results:

It was found that the V_{BBB} increased from 166.9±50 mm^3 to 218.3±50 mm^3 with an incidence angle range of 74.433±0.19° to 80.01±0.19° at 300 kPa. When maintaining both the pressure and the incidence angle fixed at 300kPa and 81.24±0.66°, respectively, the opening volume remained relatively constant (544.1±20mm^3). The squared correlation coefficient between the incidence angle, the pressure and the V_{BBB} was of the order of 0.7264, 0.8762, 0.89, 0.9183 and 0.93 for each NHP separately, while when keeping the pressure fixed, the squared correlation coefficient was found as of 0.7262, 07264, 0.8711, 0.9376 and 0.9458. The opening-to-targeting-shift varied from 2.08±1 mm to 4.2±2 mm axially and 0.7±0.5 to 2.6±2 mm laterally within a FUS beam incidence angle range of 17.4°, from 72.32° to 89.77°. Finally, the opening in the GM accounted for an average of 88.5% of the opening cases when targeting the Pu, while 78.3% occurred in the GM when focusing on the Cau.

Discussion and Conclusion:

These findings not only indicated a linear correlation between the incidence angle, the pressure and the V_{BBB} but also the consistency of the output for the same incidence angle and pressure. This enables the parametric optimization of the experimental setup to induce the desired opening and the reproducibility of the experiment. In addition, the shift from the geometric focus appeared to be independent of the pressure and incidence angle applied. Evidence provided on the feasibility of inducing opening in the gray and white matter indicate a possible cause for the geometrical shift.

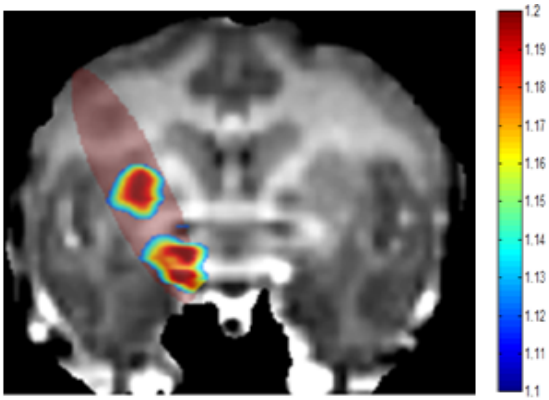

Figure1: *T1 weighted image with the V_{BBB} and targeting overlay at 300 kPa for an incidence angle of 83.23°.*

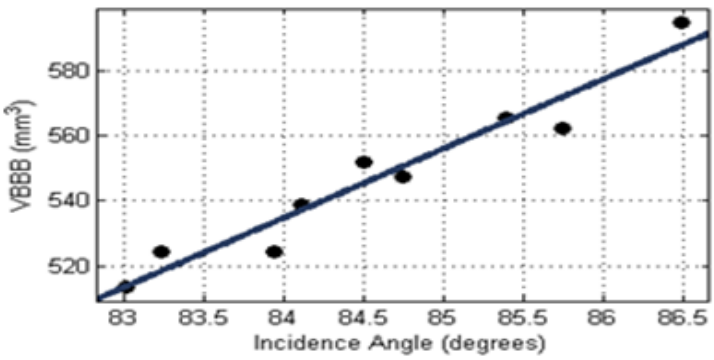

Figure2: *Linear regression of the Incidence angle and the V_{BBB} at 300 kPa.*