Blood-brain barrier disruption in nonhuman primates using a clinical MRI-guided focused ultrasound system: preliminary results

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Introduction: The purpose of this work was to perform a safety study of targeted blood-brain barrier disruption (BBBD) via ultrasound bursts combined with a microbubble agent (1) in nonhuman primates using a clinical MR-guided Focused Ultrasound (MRgFUS) system. This noninvasive technique could enable targeted delivery of substances past the BBB, which otherwise limits the use of most drugs in the brain (2). These tests aim to address potential safety issues that cannot be determined using small animals.

Methods: Our Institutional Animal Care and Use Committee approved the experiments. Sonication was performed transcranially in four anesthetized adult male rhesus macaques with the ExAblate 4000 brain transcranial MRgFUS system (InSightec, Haifa, Israel), which integrates a 1024-channel phased array (30 cm hemisphere; 220 kHz) with a 3T MRI (GE). Imaging was performed using a 15cm surface coil. Multiple locations in each animal were targeted via electronic beam steering with 70s sonications (10 ms bursts; 1 Hz PRF). At the start of every sonication, ultrasound contrast agent (Definity, 10 µl/kg) was injected intravenously via bolus or constant infusion. BBBD was evaluated in T1-weighted MRI after injection of Gd-DPTA (Magnevist, 0.2 ml/kg). The presence or absence of tissue damage was assessed with T2 and T2*-weighted imaging. Targets included the thalamus, putamen, lateral geniculate nucleus (LGN), hippocampus, cortex, visual cortex, and white matter. Acoustic power ranged from 0.3 to 10W. The pressure amplitude at the focus was measured in water and inside an ex vivo macaque skull using a calibrated hydrophone. No aberration correction was used. One animal was tested twice over 2 weeks, and one was tested 9 times over 12 weeks. Overall, 81 targets were sonicated; in 46 targets the focus was electronically steered to multiple locations during sonication to disrupt a ~1 cm^3 volume. Acoustic emission was recorded during sonication using passive cavitation detectors located adjacent to the head.

Results: It was possible to produce localized BBBD in gray matter structures without MRI-evidence of damage or any other unwanted changes outside of the target volume. Dynamic steering of the focal point produced contiguous volumes of BBBD in gray matter. MR contrast enhancement was not observed in white matter or in white matter portions of sonicated volumes. Examples are shown in Fig. 1. In gray matter structures, BBBD was observed in 61/62 locations with acoustic powers of 0.9W and above. MRI-evident tissue damage occurred at acoustic power levels of 1.5W and higher for non-thalamic, gray matter structures; such damage occurred at 1W in the thalamus. The BBBD threshold was approximately 0.75-0.90W, corresponding to estimated focal pressure amplitudes of 0.19-0.21 MPa. Both bolus injections and infusions of the microbubble agents were effective for producing BBBD. In one animal, the LGN and hippocampus were targeted multiple times with no evidence of tissue damage. It was possible to transcranially record the acoustic emission. As others have shown, acoustic emission analysis suggests that wideband emission (indicating inertial cavitation) is not required for BBBD (3,4), and real-time (~1ms) emission monitoring may provide a safety indicator. T2*-weighted imaging appeared to be sensitive for detecting petechaie in cases with overexposure. The animals recovered repeatedly with no behavioral deficits after the procedure.

Discussion: Overall, these data demonstrate the feasibility of using a clinical MRgFUS system for targeted BBBD in multiple brain structures in a large animal model without producing MRI-evident damage or unwanted effects on surrounding tissues. The BBBD threshold is similar to that found in small animals (5). The reason for no apparent BBBD in white matter is unknown, but it may be that the number and density of blood vessels is low and any MR contrast enhancement could not be detected. The apparent lower threshold of the thalamus to damage may be due to differences in tissue properties or to its central location in the brain, which may be nearly optimal for ultrasound transmission with this device without aberration correction. Future work will evaluate histological and functional effects produced by these exposures and investigate methods to guide the procedure.

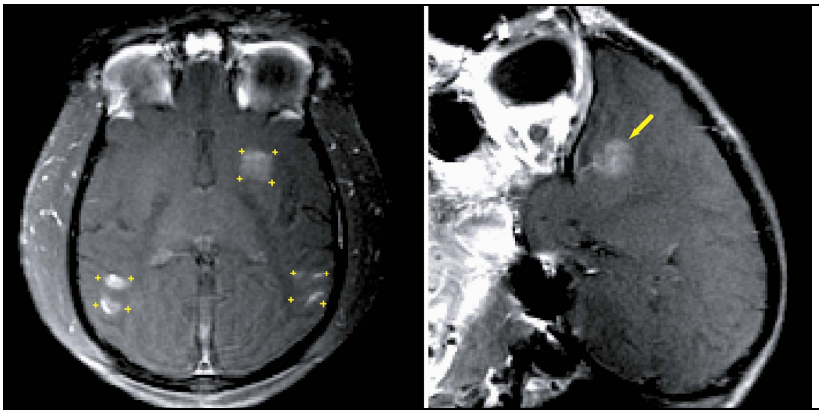

Fig 1. Contrast-enhanced FSE images of a rhesus macaque showing localized volumetric BBBD in the putamen and in two bilateral locations in the visual cortex. The focal point was steered dynamically to 9 locations in a 3×3 square pattern during sonication to target a volume. The corners of the targeted volume are shown in the axial image (left). In the putamen, a contiguous region of BBBD was observed. No effects in the beam path or at the skull base were observed in sagittal imaging (right). In the visual cortex targets, only gray matter portions of the targeted volume had evident BBBD.

References: (1) Hynynen K, et al. *Radiology* 2001; 220:640-6. (2) Pardridge WM. *J Drug Target* 2010; 18:157-67. (3) McDannold N, et al. *Phys Med Biol 2006*; 51:793-807. (4) Tung YS, et al. *Phys Med Biol* 2010; 55:6141-55. (5) McDannold N, et al. *Ultrasound Med Biol* 2008; 34:834-40.
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