Localized blood brain barrier opening of the macaque brain using a high frequency multielement Focused Ultrasound transducer array and microbubbles

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Target Audience: People interested in drug delivery combined with MRI on non human primates

Purpose

Localized Blood Brain Barrier (BBB) opening is challenging to plan on non human primates. Moreover being able to open the BBB in a restricted focal zone is a necessary step before using this method for therapies such as drug delivery. Indeed, the idea is to bypass the BBB just in small regions considered as targets for different drugs such as chemotherapies. Here we developed in house a dedicated stereotactic frame mounted on a multielement focused ultrasound array. Stereotactic images are loaded in a planning software that allows controlling the localization of the BBB opening.

Methods

Experiment was conducted on an anesthetized macaque (Macaca fascicularis). Animal was anesthetized with a mixture of Kétamine (3mg/kg) and dexmédétomidine (15µg/kg) and the anesthesia was maintained by an infusion of Alfaxan (Alfaxalone, 0.2mg/kg/min). The temperature of the animals was maintained at ~37°C using a heated water blanket. Animal physiology was monitored during the whole experiment. A homemade stereotactic frame holding the monkey head was affixed to a 512-element transducer resonating at 1 MHz (SuperSonic Imagine, France). Images were imported in a planning software in which all the positions of the head of the monkey in regard to the transducer were stored, along 6 axis of freedom (2 rotations and one translation for the transducer and one rotation and two translations for the head). One the coordinate of the target was chosen in the stereotactic frame coordinates, the planning software allowed determining the position of the frame and the transducer. MRI was performed using a 3T Siemens Verio system (Siemens, Germany). Body coil was used for excitation and an 8-channel phased-array coil (Life Services LLC, USA) dedicated to primates was used for reception. T1 longitudinal relaxation time was obtained at baseline using an MP2RAGE sequence prior to BBB opening[1]. Ultrasound excitation consisted on a 400 kPa Peak Negative pressure sinusoidal tone burst of 10 ms, with a pulse repetition frequency of 1 Hz during 120s. Excitation was started following a bolus injection of 1.5 mL of Sonovue (Bracco, Switzerland) and lasted for 2 minutes. A bolus of 1.5 mL of an MRI contrast agent (Dotarem, Guerbet, France) was injected 5 minutes after the end of ultrasound excitation. A second MP2RAGE dataset was obtained 10 minutes after contrast agent injection to monitor the localization of the BBB opening resulting in a T1 decrease in the region of interest (ROI) induced by the contrast agent.

Results

A first pilot study was conducted in a living macaque. After BBB opening, T1 decrease was clearly obtained in the ROI defined by the planning software (Figure 1), indicating that BBB was opened in the targeted ROI. T1 values were 1000 +/- 70 ms before and 662 +/ -31 ms after the HIFU procedure resulting in a ~33% decrease in T1. The size of the area of BBB opening was 3.2 mm in diameter and 5.6 mm depth. After the experiment, the animal recovered and no side effects were observed during the 3-week follow-up.

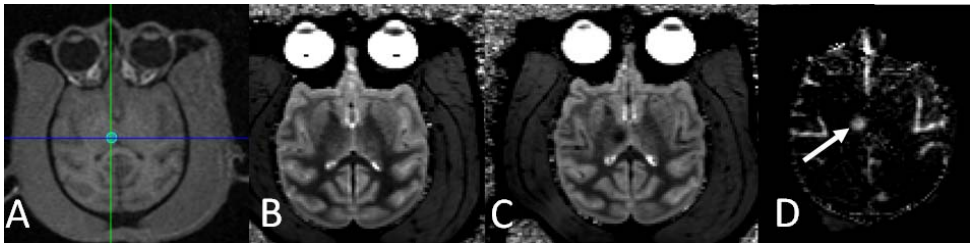

Figure 1: A. Planning software and target ROI definition. B. T1 map before BBB opening. C. T1 map after BBB opening. D. T1 difference between both images, arrow indicates the BBB opening on the targeted ROI

Discussion

The procedure allowed successful transient opening of the BBB in a small ROI in a living primate with no side effects. This study will be replicated in other animals with the long-term objective of developing a system suitable for human applications.

References

1. Marques JP, Kober T, Krueger et al. MP2RAGE, a self bias-field corrected sequence for improved segmentation and T1-mapping at high field. Neuroimage 2010 15;49(2):1271-81