Inflammatory response and cognitive function following focused ultrasound-mediated blood-brain barrier opening in non-human primates

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Background, Motivation and Objective

Focused ultrasound (FUS)-induced blood-brain barrier (BBB) opening is currently being tested in clinical trials. Pre-clinical studies in rodents treated with FUS have shown an acute inflammatory response, which is resolved within 7 days after treatment. Here, we investigated the acute and chronic inflammatory response in non-human primates (NHPs) treated with a clinical FUS system. Behavioral testing was also conducted to assess cognitive function following clinically-relevant BBB opening.

Statement of Contribution/Methods

Four NHPs were treated in the prefrontal cortex (PFC) using a neuronavigation-guided single-element FUS transducer (f_c: 0.25 MHz, $P_{pk\text{-}neg}$: 200 - 400kPa, MI: 0.4 - 0.8, PL: 10 ms, PRF: 2 Hz, duration: 2 min) and the FDA-approved dosage of Definity microbubbles (10 µl/kg). Two NHPs were treated bilaterally (MI: 0.4 and 0.8 - left and right PFC), and were sacrificed at the acute (2 days post-FUS) and chronic (18 days post-FUS) timepoints. Their brains were extracted, sectioned and stained for Iba1 and CD68 to evaluate microglia presence and activation. Two NHPs performed an inference test for 4 weeks before FUS treatment and were then treated unilaterally (MI: 0.4 and 0.8 - left PFC). Behavioral testing using touch panels was conducted daily for 3 weeks post-FUS to evaluate changes in touch accuracy and reaction times.

Results/Discussion

Clinically-relevant FUS treatments led to BBB opening volumes (fig. 1a) of 680 ± 236 mm^3 at MI of 0.4 (n = 3), and 1413 ± 299 mm^3 at MI of 0.8 (n = 3). Density of $Iba1^+/CD68^+$ cells within regions exposed to FUS was higher ($p<0.05$) than in non-treated areas only at the acute timepoint and MI of 0.8 (fig. 1b). BBB opening at MI of 0.4 moderately increased inflammatory cell density ($p>0.05$). By day 18 post-FUS, cell numbers were restored to baseline for both MI ($p>0.05$). The increased number of cells at MI of 0.8 was due to microglia migration towards the periphery of blood vessels, indicating a repair mechanism to restore homeostasis during BBB closing (fig. 1c). Average accuracy increased for both NHPs (figs. 1d and e), but significantly only at MI of 0.8 ($p<0.05$). The reaction time increased at MI of 0.4 ($p>0.05$), but significantly decreased at MI of 0.8 ($p<0.05$). These results demonstrate that FUS-induced inflammation is triggered at high MI but is reversible, while BBB opening may be associated with improvement in NHP cognitive performance.

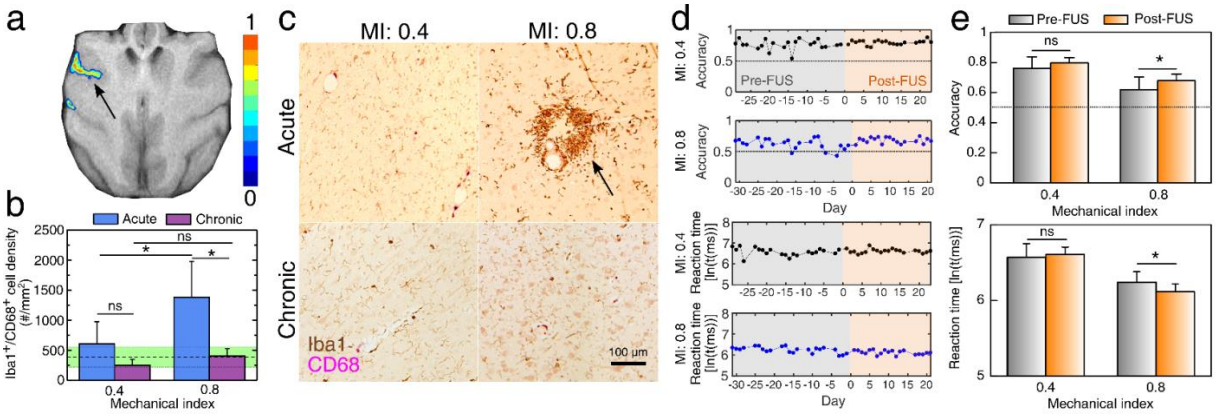

Figure 1: a) BBB opening in the prefrontal cortex of a NHP (MI: 0.8). b) Inflammatory cell density within the targeted area after FUS treatment. Green shaded region: baseline density in a non-treated area. c) NHP brain slices stained with Iba1 and CD68, showing migration of microglia. d) Daily and e) time-average accuracy and reaction time before and after FUS treatment. Dotted line: responses by chance. Data presented as mean ± standard deviation.*: $p<0.05$, ns: non-significant.