Tests of microbubble-enhanced ablation in a large animal model with a low frequency, transcranial MR-guided focused ultrasound system (FUS144, PI: Nathan McDannold)

Progress Report

We have completed the experiments proposed in the grant and are now going through the data to prepare for a publication. As we describe below, we had some significant issues in achieving the goals of the grant as specified in the proposal. However, we ultimately were successful and were able to gather data that we think will be of great interest to the FUS community.

"Exciter/Ablator" experiments

We had planned on testing microbubble-enhanced thermal ablation of central structures in the brain in non-human primates using the low-frequency ExAblate transcranial MR-guided FUS system. We hoped that these experiments would allow us to understand how these lesions develop over time. Our goal was to understand whether what happened to a patient (delayed hemorrhage) was a natural fate for this type of ablation.

With this type of ablation, a high-intensity burst is applied to generate a cloud of microbubbles at the focus. Subsequent sonication at a lower intensity is then applied, and the bubbles should effectively increase the absorption coefficient, leading to significant heating and tissue ablation. If this technique is successful, this approach could greatly expand the "treatment envelope" where one can transcranially ablate without overheating the skull bone. We proposed to test this technique in five monkeys.

We first attempted this type of ablation using an older version of the ExAblate software. "Exciter" pulses are used to initiate cavitation; "Ablator" pulses are used to generate heat. Tests were performed in two monkeys with relatively long (10-40ms) Exciter pulses and 1s Ablators. We first measured the cavitation threshold at the targets using only Exciter pulses. We observed clear wideband emission at 120 W acoustic power and 10 ms pulses. We then evaluated Exciter/Ablator sonications at increasing power levels and Exciter burst lengths. Despite seeing substantial wideband emission during the Exciters and sustained cavitation activity during the Ablators, we did not observe enhancement in the focal heating, and no evidence of hemorrhage was observed in post-sonication T2*-weighted MRI. Furthermore, brain surface heating was determined to be dangerously high, so we did not want to increase the power.

We suspected that perhaps the cavitation activity was occurring somewhere else (in a ventricle, for example) and that if we could use higher power levels and shorter Exciter bursts that we could exceed the cavitation threshold at the focus and achieve microbubble-enhanced ablation. The older software version did not support this, and we arranged to have InSightec install the updated software. This caused a delay of more than five months.

After receiving the new software and learning how to use it, we continued this work in two additional monkeys using shorter (100 μs) Exciter bursts. Again, the cavitation activity recorded during the sonications was exactly like one would expect: wideband emission during the Exciters and sustained cavitation activity during the Ablators. However, again we saw no evidence that the focal heating was enhanced in any meaningful sense, and we did not see evidence of hemorrhage that one would expect

with large inertial cavitation in T2*-weighted MRI. We sonicated as high as 3000 W acoustic power.

We surmised that either we are cavitating in the water bath, or that there is some issue with the system output at high power levels. To test whether we are cavitating in the water bath, we performed an experiment in which we sonicated an ~8cm diameter solid rubber ball, where no cavitation at the focal point would be expected. While we are still analyzing the spectral data, wideband emission was observed at the highest power levels, suggesting that perhaps that cavitation activity was occurring in the water during our monkey experiments. These tests were performed in three monkeys.

Our (tentative) conclusion is that either the cavitation threshold in the normal brain is higher than what this system can deliver during transcranial experiments in monkeys, or that shielding induced by microbubbles in the water attenuates the beam and limits the amount of energy that can be delivered to the focus. Note that if this shielding is occurring, it does not mean that this approach cannot work in humans. The monkey's head is substantially smaller than a human's, and the acoustic intensity in the water bath just outside the head will be lower than was the case in the monkeys.

Over the duration of the grant, we will be analyzing the MRI, spectral, and histological data obtained in these five monkeys to determine if (1) we can make a firm conclusion about our negative outcomes and (2) if these results are publishable.

"Non-thermal" ablation using FUS and injected microbubbles

In our first three sessions with Exciter/Ablators (in two monkeys), after failing to achieve thermal ablation at the thalamus, we performed additional sonications combined with an ultrasound contrast agent (Definity) and low-intensity, low-duty cycle sonications to ablate deep brain structures. This method was utilized in the PI's prior FUS Foundation grant. We found that we could achieve this ablation at targets in the amygdala adjacent to the optic tract. The lesions were well-defined, and no evidence of thermal damage was observed. Furthermore, even when the focal region overlapped with the optic tract, damage to the nerve itself was minimal (presumably due to its relative paucity of blood vessels).

During the time when we were waiting for the updated software from InSightec, we repeated the experiment in an additional monkey. Finally, we had one last monkey that we were going to test for this grant. However, it was found to have a metal object in his brain (it turned out to be a pellet from a shotgun) that precluded our use of MR thermometry, so we could not test the Exciter/Ablator sonications. We were able to test this "non-thermal" ablation method, as it does not require MR thermometry. Thus, overall, we were able to test this technique in four monkeys.

We will be spending the rest of the grant period going through the histology (which is quite laborious in the large monkey brain), MRI, and spectral data obtained during these experiments, after which we will submit this study for publication. We have submitted it to present at this year's upcoming FUS Foundation meeting. The results we have obtained in this study were used as preliminary data for an R01 application. It received a highly favorable score (6^{th} percentile) and we are optimistic that it will be funded.

To conclude, we have performed the work outlined in the grant proposal. However, the results have been disappointing. However, we were able to do additional experiments with “non-thermal” ablation that have been highly successful and were the basis for beginning a long-term project that (we hope) has been funded by NIH.