Brain Workshop 3

Overview and Attendance
The Focused Ultrasound Surgery Foundation’s third Brain Workshop convened from October 23rd through the 26th and was attended by 77 participants from 12 countries representing about 30 different institutions, companies and government agencies. Leaders in the field presented recent findings and status updates on clinical, preclinical, and technical research projects. Projects were also discussed that should be planned and executed before the next Brain Workshop in order to accelerate the clinical adoption of MRg-FUS. This white paper provides an overview of the topics of discussion and the outcomes of the meeting in terms of working groups established and outlined plans of research activity over the next 1-2 years.

Clinical Status

Essential Tremor (ET)
ET is the most common movement disorder in the world, occurring with a prevalence 5-10 times that of Parkinson’s disease (PD). Although often considered benign, in patients with severe symptoms and failure to respond to medication it is a very disabling condition, limiting or preventing patients from performing their activities of daily living. Additionally, there are not many good treatments for the disorder. Concerning suitability for FUS, the target (thalamus) has a deep location and lies well within the treatment envelope. Prior work in Zurich and Boston has proven feasibility, and the ventralis intermedius has a long history of being effectively lesioned for tremor.

University of Virginia (Jeff Elias, Diane Huss, Max Wintermark)
The objective of the UVa pilot trial was to demonstrate the safety and feasibility of unilateral lesioning of the VIM nucleus with MRgFUS and the currently available stereotactic targeting apparatus. This will also serve to supply the pilot data necessary to conduct further clinical trials. The patients chosen were those with pure ET (no PD) who had failed medical management, had significant disability (inability to dress, eat, etc …), and no significant medical comorbidities. Patients who were too ill for surgery were not chosen because these patients would have the highest risk for complications. Instead the study group consisted of people who were disabled and could have been candidates for surgery, but were interested in trying another method of treatment. A summary of the trial is provided below.

In addition to the tremor control, this trial has illustrated the potential utility of FUS to provide intraoperative physiological feedback for personalized targeting. In one patient parasthesias were observed during the initial sonications. Given the location of the VIM between the sensory and motor portions of the thalamus, this signifies slight misposition of the target. An adjustment of 1.5 mm allowed lesioning providing good tremor control and no further symptoms. This, in addition to the functional MRI data reviewed supports the possibility of FUS to be used as a tool for diagnosis, neuromodulation, and improved target mapping (versus atlas-based targeting).
demonstrates the accurate control of the focal location as well as the ability to elicit tissue response at sub-lethal heating levels, avoiding permanent damage while optimizing the target.

**Summary:**

- 11 patients (9 men, 2 women) [Note: Recruitment and treatment of all 15 patients for this pilot study was completed in December of 2011]
- Average age 67 years old
- Average duration of disease was approximately 35 years
- 12-24 sonications per patient, treatment time is approximately 3 hours.
- Sonications elicit temporary symptoms at peak temperatures of 45-50 degrees, permanent lesions at 60 degrees
- Side effects: typical of thalamotomy (sensory disturbance, imbalance, fatigue)
  - Nine patients reported paraesthesias; however, only one patient has ongoing symptomatic sensory disturbance (dysesthesia of the index finger).
- Assessment: Clinical rating scale of Tremor (observational & task specific) and QUEST (Quality of life assessment)
  - Scores largely stable over follow-up period
  - Mean of 63% improvement in first 10 patients (bilateral score)
  - 75% improvement at 3 months on the treated side
  - On the self-rated scale patients reported an average of 80% improvement between baseline and 3 months
  - 64% improvement in head and trunkal tremor
- Results have been relatively durable, but there is a stronger effect in the first week, likely related to perilesional edema. One patient has had a decrement in treatment effect.

**Imaging Findings**

- MRI data is only available for the first 5 patients
- No significant relationship between imaging characteristics and outcome
- No significant vasogenic edema
- No consistent relationship between repositioning of target and lesion configuration (figure of eight shape seen in 1 patient)
Solothurn (Daniel Jeanmonod)

There has been only one patient treated for ET to date. This was an 80 year old gentleman with a history of DBS implantation that was removed for infection. The centrothalamic tract was targeted which is just inferior to the VIM (the VIM itself was targeted in the UVa study). Mean and peak temperatures of 55 and 59 degrees respectively were achieved. A good clinical result was observed. This target is of interest because it has the potential to allow bi-lateral treatment whereas the VIM is bound to be limited to unilateral treatments.

This case provided proof of concept for the effectiveness of MRgFUS for ET in patients who have undergone previous DBS therapy.

Questions/Issues

- What is the optimal lesion size?
  - When is the lesion measured (acute versus late)?
  - Radiofrequency ablation produced lesions with a diameter of 4-5 mm
- What is the optimal target location (centrothalamic tract versus ventralis intermedius)?
  - Possible need for double lesioning when using the VIM?
- Optimal method for target identification?
  - Atlas versus functional MRI or DTI
  - Intraoperative neurophysiological verification via neuromodulation
- What is the cause and duration of MR contrast enhancement?
  - In the UVa experience, there is contrast enhancement at 1 month. Does this mean that the blood brain barrier remains open for this duration after treatment or does this represent an inflammatory reaction?
- Can treatment duration be reduced?
  - Calibration, alignment, and power titration takes several hours with the present system and software configuration
  - Transducer position requires manual readjustment
  - Necessity of CT for skull correction (MR Ultrashort TE (UTE) sequence in research stage for bone imaging)
  - Volumetric thermometry (as opposed to single plane thermometry)
- Is bilateral lesioning and combination with DBS feasible and safe treatment options?
- Ventrolateral thalamotomy carries higher risk with traditional methods, although this technology may allow testing prior to lesioning with non-thermal neuromodulation parameters.

- Lesioning contralateral to a DBS electrode is likely more feasible in the short-term.

**Parkinson’s Disease (Daniel Jeanmonod)**

MRgFUS remains in the early stages of evaluation for PD. Three patients have been treated to date in Solothurn with encouraging results. The population includes 2 males and 1 female with a disease duration of 11-27 years. The target is the pallidothalamic tract, as this is felt to offer better improvement over the range of kinetic symptoms with a smaller & safer lesion. Although, there is some suggestion that treatment may slow progression of cognitive symptoms, the acceptable indication for treatment remains movement related disability.

Initiation of a pilot study for tremor predominant PD is planned at UVa, to occur in parallel with the trial at Solothurn.

**Neuropathic pain (Daniel Jeanmonod)**

Twelve patients have been treated in Zurich with MRgFUS for neuropathic pain. This represents the seminal clinical work on transcranial FUS. The largest population for treatment would be those with amputations, of which 5-10% will develop chronic neuropathic pain. In the current group, the average duration of symptoms was 8.5 years. All patients were treated with a centrolateral thalamotomy. There is evolution of treatment effect over time with the greatest being seen at one year follow-up (currently 58% improvement). While patients experience nausea, emesis, and other vestibular symptoms during sonication (similar to RF), there has been only one permanent neurological complication. This occurred in a patient who suffered a hemorrhage and cavity formation. The patient has largely recovered, but does still have some motor symptoms and neglect under times of stress. The targeting accuracy was also evaluated with 85% being within one millimeter of the target. No evidence of lesion growth was seen over the 18 month follow-up.

**Brain Tumors (Edward Oldfield)**

Intracranial tumors remains a significant challenge both in terms of difficult locations (deep-seated lesions or those in close proximity to critical structures as in the cavernous sinus) and for those patients who have failed other modalities. MRgFUS holds great potential; however, it remains in the early stages of development with regards to this application.

**Sunnybrook (Todd Mainprize)**

Intracranial metastases occur in 30-50% of those with cancer. These lesions are currently treated with surgical excision if possible, whole brain radiotherapy, and Gamma Knife. The study in Sunnybrook has been open for enrollment for 6 months, but has not enrolled any patients to date due to the limitations of the inclusion criteria. Currently they are including patients who are not candidates for other therapy and
this has a significant impact, as patients are often able to receive palliative radiotherapy. Additionally, the lesions must be small and located more than 2.5 cm from the skull. The issue of treating posterior fossa lesions was raised; however, these patients are at greater risk for complications due to bone heating and the consequences of swelling. As such, they are not felt to represent good candidates for a safety and feasibility study.

**Zurich (Martin/Fandino)**

Mimicking the concerns addressed above, there have been difficulties in enrolling patients due to restrictive inclusion criteria (Karnosfksky Performance Status (KPS) > 70, size < 3.0 cm, > 2.5 cm from the skull, able to tolerate treatment). Also, many of these patients require implantation of foreign bodies (cranioplasty flaps, shunts) or have an adjacent cystic cavity, both of which have an unknown effect on treatment.

**General Discussion**

Tumor selection represents a challenge. Invasive tumors have poorly defined margins and cannot be treated in entirety. Those benign lesions that are clearly defined and could be treated are poor candidates given the close proximity to the skull, in addition to the consequences/risks of complications in these patients. While the current purpose is merely safety and feasibility, there is concern that treating gliomas is risky (based on the experience at the Brigham) and offers no or little benefit to the patient. Metastases are felt to represent a more preferable lesion for initial trials.

**Preclinical Status**

**Ischemic Stroke (Thilo Hoelscher)**

Stoke is a major source of morbidity and mortality worldwide and the application of tPA is limited. The concerns for MRgFUS share some of those that limit the application of tPA. The current limit of tPA is 4.5 hours and this envelope is extended to 6 to 8 hours for interventional thrombectomy in the anterior circulation and 24 hours in the posterior circulation. Many patients present outside of these windows; therefore, MRgFUS would have to compete with this limited population.

One solution would be to expand the scope to include treatment of downstream microcirculation instead of recanalization of the occluded artery. This has the theoretic potential to expand the population; however, it would introduce additional concerns about the effect of sonication on ischemic tissue. Discussion suggested a focus on reducing infarct size rather than just recanalization. Possible mechanism is that the combination of microbubbles and focused ultrasound stimulates nitrous oxide release, which in turn promotes angiogenesis.

Monteith et al at UVa have developed a cadaver model on which an angiogram and MRA can be performed to monitor treatment. A clot was placed in the middle cerebral artery and recanalization was demonstrated after sonication. This model also demonstrated that the basilar artery is a feasible sonothrombolysis target.
Intracerebral Hemorrhage/Intraventricular Hemorrhage (Stephen Monteith)

Stroke remains a leading cause of morbidity and mortality worldwide and the treatment options, especially for hemorrhagic stroke remain limited. In vitro, in vivo swine and cadaver models have been used to demonstrate feasibility of using MRgFUS to liquefy an extra vascular blood clot in the brain under MR monitoring with subsequent percutaneous aspiration. The goal would be lysis of 80-90% of the clot, leaving a surrounding rim to help prevent rehemorrhage. These studies have been performed using the 220 kHz ExAblate 4000 system without evidence of BBB disruption or surrounding tissue damage (both radiological and histological evaluation).

- Clot atlas complete. Clot signal history per over several MR pulse sequences was collected. T2 weighted sequences were the most helpful in visualizing clot lysis by increased T2 signal.
  
  In vitro w/ skull: 10% duty cycle, 1 KHz pulse repetition rate, 3920 W

- Needs for clinical trial
  - Improve acoustic intensity at the focus by: more power, netter focusing, more effective sonication pattern
  - Complete follow-up on in vivo safety data
  - Newel technique with Ekos catheter plus TPA is a possible competitor?
    - Infection hazard
    - Catheter breakage
    - Can’t lyse as much volume
    - No real-time monitoring of catheter tip

Blood Brain Barrier Opening + Drug Delivery

Chemotherapy for glioblastomas (Todd Mainprize)

A phase I clinical trial is expected to begin in the next few months evaluating the feasibility of MRgFUS and microbubbles for blood brain barrier (BBB) disruption in patients with newly diagnosed glioblastoma multiforme (GBM). GBM is the most common primary brain tumor in adults affecting approximately 17,000 people in the US each year. The average life expectancy associated with this diagnosis is 14 months. The current treatment paradigm involves maximal safe surgical resection, external beam radiation therapy (XBRRT) (55-60 Gy), and concurrent temozolamide. The proposed study would include all patients who are candidates for surgical resection. Sonications would be performed within the tumor as well as in the surrounding non-enhancing region. The proposed medications for delivery include doxyrubicin and/or taxol. MRI with and without Gadolinium as well as histology following surgical resection would be used to characterize the extent of BBB disruption and associated drug concentration.
Given the broader inclusion criteria, recruitment is expected to be easier than with the other ongoing trials.

An important consideration for the future is that the BBB disruption that occurs is maintained for 6 to 24 hours, so depending on the pharmacokinetics of the medication administered, sonications could be required on a daily basis.

Several preclinical studies were presented concerning safety and the ability to deliver different biological and pharmacological agents:

- Amyloid plaque antibody delivery for Alzheimer’s Disease
- Brain-derived neurotrophic factor (BDNF) delivery in monkey brain
- Hynynen: Stem cell delivery for Parkinson’s Disease
  - Fluorescent tagged stem cells have been delivered via MRgFUS BBB disruption and these cells appear to remain active after delivery. This has been performed safely without evidence of vascular damage or red cell extravasation.
  - Concerning monitoring, 1st and 2nd and half harmonic detection has been used to monitor/control power for safe BBB disruption.
  - It is not clear how cells cross the open BBB
- McDannold: BBB opening in Macaque monkeys
  - A feasibility safety study of BBB disruption was performed in seven rhesus macaques using the ExAblate 4000 low-frequency brain system.
  - Burst sonications (10 ms bursts at 0.6 Hz) were applied transcranially over a range of acoustic power levels to 185 brain targets over 33 sessions. Three 50 s sonications were applied over 200 s at each target. Sonication began simultaneously to an infusion of diluted Definity (10 µl/kg) that lasted for the entire sonication time. Electronic beam steering was used during each sonication to target multiple focal regions with each sonication.
  - BBB disruption was evaluated using MRI contrast enhancement. Damage was detected using T2*-weighted MRI and histology. Three animals underwent functional testing after five weekly BBB disruption sessions in targets in the visual system.
  - It was demonstrated that BBB disruption was feasible without significant vascular damage evident in post-treatment MRI or in histology. MRI contrast enhancement was not observed in white matter, but was observed post-mortem after injection of trypan blue.
  - No functional deficits were observed resulting from the sonications.
• The disruption was contained to the targeted volume, with the exception of when sulci or ventricles were targeted. It is recommended that sulci and ventricles not be sonicated, as they may pose a risk for drug delivery to non-targeted regions and potentially for damage.

• Acoustic emission was monitored using in-house built passive cavitation detectors and appear promising for safety monitoring (through evaluation of broadband emission) and potentially for control over the procedure (through monitoring of harmonic emission).

• This work supports the initiation of clinical trials for the delivery of chemotherapy agents to brain tumors using the low-frequency ExAblate 4000 system.

• For clinical readiness, software modifications are needed for the ExAblate system to calibrate it at the low acoustic power levels used for BBB disruption (1W or less in the macaques) and operate in burst mode. Modifications to the acoustic emission monitoring system were also recommended so that harmonic emission can be evaluated.

**Temporal Lobe Epilepsy (TLE) (Stephen Montieth)**

Preliminary data was presented regarding the feasibility of FUS for ablation in TLE. Using a cadaver model, a nine degree thermal rise was achieved in a region corresponding to a selective amygdalohippocampectomy. With the 220 kHz system, ablation of this area was easily feasible, whereas with the 650 kHz system modification to the stereotactic headframe was necessary.

**Questions/Issues**

- Cavitation detection safety
- Skull base heating (seems feasible based on the trigeminal neuralgia (TN) data)
- Volume necessary (Dr. Quigg suggested a volume of 5.5 to 6.5 ml would be necessary, something likely too large to be treated in one setting with the current ExAblate 4000 650KHz unit). It was suggested that perhaps disconnection of the associated tracts rather than ablation of the entire region could be performed; however, this will require further investigation
- Clinical Recruitment
  - The ROSE trial (Mark Quigg) has been enrolling for 2 years and has only been able to enroll 30 patients. The patients for FUS would be of the same population. Enrollment is felt to be poor due to improved tolerability of antiepileptic medications, as well as the performance of “routine” epilepsy surgery outside of the academic realm.

**Neuromodulation (Seung-Schik Yoo and Mickael Tanter)**

MRgFUS, as demonstrated in the ET patient described above, and in animal models has the potential to allow identification of functional neurological units in a reversible fashion. This would allow more precise definition of targets for ablation, in addition to the potential for improvement in understanding of neuroanatomical structures. At present, research has been conducted in large and small animal models
using pulsed, low intensity, low acoustic pressure sonications, as presented by Seung-Schik Yoo. Mickael Tanter introduced a novel ultrasonic method to image brain activity, based on ultrafast Doppler imaging. Epileptic seizures on rats have been imaged with this techniques and could promisingly be used to investigate the neuromodulated activity of the brain. The results and future directions are summarized below.

- Rodent and rabbit models have demonstrated the ability to stimulate motor cortex as well as the abducens nerve. The latter has implications for the stimulation of white matter tracts in addition to nuclei.

- In a rodent epilepsy model, sonications have been able to terminate seizure activity. This could potentially be used in a clinical model to define a seizure focus prior to ablative sonications.

- Sampling of tissue following sonication has demonstrated changes in neurotransmitter concentrations.

- Sonication of the thalami in animal models have shown more rapid emergence from anesthesia.

- Technical issues:
  - Optimal sonication parameters to achieve stimulation versus suppression
  - Treatment envelope
  - Dimensions of focus
  - Non-thermal localization of focus (ARFI)
  - Long term effects in large animals/humans?, BBB disruption?, temperature increase?

**Trigeminal Neuralgia (Stephen Monteith)**

Although many therapeutic options exist for the management of TN, there remain those refractory and/or unsuitable for these modalities. In addition, this work serves to expand our understanding of the treatment envelope. An ex vivo skull with implanted thermocouples and cadaver model have demonstrated the feasibility of sonications with MRgFUS in this region.

- Thermal spot and temperature rise achieved on root entry zone of the TN

- Blocking of the petrous bone (selective deactivation of transducer elements) reduces bone heating (IAC 17 vs 6 degree rise, cisternal 17 vs 5 degree rise)

- Basilar artery seems safe, minimal clivus heating
Technical Status

Remote effects

Following the discussions at the first and second Brain Workshop, there was concern that standing waves effects and unintended heating remote from the focus could be a substantial safety risk.

Kullervo Hynynen presented the results of simulations and experiments performed à 220kHz showing that the fluctuation pressure amplitude would be greatly reduced by using a large-scale, hemispherical phased array with a low f-number (as published in Song J, Pulkkinen A, Huang Y, Hynynen K. IEEE Trans Biomed Eng. 2011).

Jean-Francois Aubry presented simulations conducted at 220kHz, 660kHz and 1MHz in a central location of the brain. In order to be able to compare the volume at risk, the volume of the brain that is above a Mechanical Index (MI) threshold, as a function of the MI. The advantage of using the MI as an index is that it is frequency-scaled and that it allows all potential users to select the threshold for the risk associated to their application, given the sonication parameters (pulses or continuous) and the presence of absence of standing waves. On average, compared to 220Khz, the volume at risk is one hundred times smaller at 660kHz and one thousand times smaller at 1MHz. Nevertheless, this is due to the main lobe and not to secondary hot spots, except for high power sonications in the vicinity of the skull base. Comparison between 220kHz and 1MHz has been published (G. Pinton, J.-F. Aubry, M. Fink, and M. Tanter, Numerical prediction of frequency dependent 3D maps of mechanical index thresholds in ultrasonic brain therapy, Med. Phys. 39, 455:467 January 2012). Ongoing work is addressing the use of each frequency in central, near skull base and near skull vault targets. Further work could investigate the fraction of standing waves in order to consolidate Song et al conclusions.

Both studies in Toronto and Paris are expected to be completed in 2012.

MR Acoustic Radiation Force Imaging (MR-ARFI)

Several groups are actively working on MR imaging techniques which are sensitive to the small tissue deflection that occurs at the focus during focused ultrasound sonication. Tissue motion on the order of micrometers can be visualized with this technique, allowing both the focus location and the focus quality to be measured. In addition, the following benefits can also be realized with MR-ARFI:

- Focal spot verification with one tenth the energy of thermal focal spot verification and virtually no heating.

- Anatomical imaging and spot visualization with a single pulse sequence. Unlike proton resonance frequency shift (PRFS) thermal imaging, registration error is not a concern, as MR-ARFI requires no registration with a separate anatomical image.

- MR-ARFI acquisition can be added to existing standard spin echo and echo planar pulse sequences.
MR-Based Focusing

Clinical MRgFUS brain systems currently require a high resolution CT scan to be acquired prior to treatment in order to correct for skull aberration. Research is underway to provide an “auto-focusing” capability through the use of MR-ARFI as a real time measure of focus quality with the goal of making CT scans potentially unnecessary. There are several optimization methods being researched that involve iteratively adjusting the output of transducer elements according to various basis functions and measuring the effect on the focus with MR-ARFI. It was shown by the Intitut Langevin and Stanford groups that, given sufficient time, these approaches can achieve better focus quality than CT-based simulation approaches. It has yet to be demonstrated whether the process can be made fast enough to be clinically feasible, and that SNR in transcranial in-vivo situation is sufficient for robust clinical use.

Volumetric Thermometry

MR thermometry considerations for MRgFUS treatments are highly dependent on the organ and application of interest. Proper monitoring of transcranial MRgFUS procedures has its own unique set of requirements, advantages, and challenges. While temperature monitoring in the brain is generally not adversely affected by motion or the presence of fat, the challenge for transcranial MRgFUS thermometry lies in the large amount of temperature measurement data that must be rapidly acquired to satisfy spatial resolution, temporal resolution, and volume coverage requirements. Similar to other MRgFUS applications, transcranial procedures rapidly deposit energy into a small volume in such a way that necessitates imaging at ~1x1x3 mm spatial resolution and ~2 seconds temporal resolution to accurately measure and track the induced temperature changes.

Unlike other applications, transcranial treatments have three unique aspects that conspire to impose the additional requirement of large volume coverage. First, transcranial ultrasound transducer arrays have large apertures that spread out the energy to improve focusing through the skull, but also create a large volume beam path over which energy may be deposited. Second, bone is highly reflective and absorptive of ultrasound, meaning that heating may occur at skull/tissue interfaces even where the ultrasound amplitude is relatively small. Third, the critical nature of brain tissue, and potentially severe consequences resulting from damage, make it imperative to monitor all areas where ultrasound energy may be deposited.

Due to the inherent trade-offs between spatial resolution, temporal resolution, and volume coverage in MR imaging, it is challenging to simultaneously satisfy all three requirements. Methods for achieving the goal of temperature maps with high spatial resolution, high temporal resolution, and large coverage generally follow one of two complementary approaches: acquire data faster, or acquire less data and use various methods to reconstruct images from under sampled data. For the former approach, the use of echo-planar imaging (EPI) to acquire several lines of k-space per excitation is commonly employed, but other more complicated k-space sampling trajectories, such as spiral imaging, have not been fully explored for thermometry. Much more research has gone into the latter approach of reconstructing images from under sampled data. Reconstruction techniques included parallel imaging, UNFOLD, constrained reconstruction methods, and methods that incorporate information from more sophisticated modeling of the temperature dynamics. Each approach has its pros and cons, but none has reached the point of fully solving the problem.
Treatment Envelope

Treatment Envelope refers to the cranial volume throughout which extracranial FUS may effectively deliver therapeutic effect. This envelope will be specific to each skull shape, thickness, and material properties, and may be different when considering ablation vs. cavitation vs. drug delivery. Matt Eames at the Foundation has begun working with custom-molded thermal acoustic gel material and ex-vivo skulls in order to map the ablative treatment envelope with two or more specimens. Thus far his results indicate that heating is most efficient near the center-of-mass of the brain, with local minima near the inside surface of the skull which arise as a result of bone heating and radiation of that energy into adjacent brain tissue. It may be advantageous to use this phenomenon for the treatment of surface METs, but it remains to be seen whether this approach would be clinically viable as levels of skull and dura heating may not be acceptable. Further studies will be conducted by Foundation staff in order to fully map the intracranial volume of 2 or more ex vivo specimens in order to increase our understanding of treatment envelope limitations and the challenges associated with extending the envelope by transducer apodization and positioning.

The treatment envelope is a tradeoff between how much energy needs to be deposited at the focus and how it is distributed over the array and the skull. The following are the key elements that were discussed:

- How much energy needs to be delivered to the focal point (varies with frequency and with target tissue)?
- How good is the focusing quality with respect to ideal situation (depends on frequency, phased array design, algorithm etc.)?
- How much energy can effectively traverse through the skull (depends on frequency, geometry, skull attributes)?

The ExAblate 4000 assessment has been presented and thresholds described.

Cavitation

There is a recognized need to further explore our ability to control – likely through real-time passive cavitation detection (PCD).

In the previous workshop, the risks and evidence of cavitation have been discussed. As a result it was agreed that all clinical treatments would monitor cavitation for safety reasons. This was achieved and implemented in all clinical studies. Additional research work may complement the industry developed tool to map safety thresholds and the impact of skull variability.

This is the foundation under which FUS-initiated cavitation with the 220kHz ExAblate system will enable more rapid treatment of large volumes in a safe manner. Little progress has been made in this area since the previous Workshop, but at least one project in this area is being funded into 2012.

MR Bone Imaging

Max Wintermark presented his prospective MR study on bone imaging. He presented SSFP/Fiesta, Cube, and 3D GRE imaging samples to illustrate the quality of bone information in each of these clinically-
approved MR pulse-sequences. The conclusion is that T1-weighted sequences provide better information about bone. Ultrashort TE (UTE) sequences will likely trump all currently available sequences, but until it is approved for clinical imaging it is not a realistic option.

**MR RF Coils**

Beat Werner and the Zurich team have worked with Rapid, a German MR coil development company, to develop a receive-only clinical head coil that mates with InSightec’s current model of brain transducer. It is designed to fit closely to the active ultrasound array, and required a modification to the ExAblate housing to permit this close fit. The group is pleased with the imaging results, and also point out that the closeness of fit permits relatively unobstructed movement and positioning of the ExAblate transducer for targeting. Although cost of fabrication was not explicitly discussed, as it was a research coil project resulting in a one-of-a-kind product, a relatively high price point may be expected.

Matt Eames and the FUS Foundation are funding the development of an animal-specific head coil for pre-clinical research with a coil design company HighField, LLC, based out of St. Paul, Minnesota. With the recent acquisition of the GE Research Key for the UVa FUS Center, initial prototype coils are expected to be tested early in 2012. First to be tested is a rabbit coil followed by the design and testing of a coil for pig imaging.

**Future Plans**

**Technical**

The treatment of Brain Tumors with MRg-FUS remains an area of great interest due to the potential to address an unmet need. However several technical challenges remain to be solved before such treatments can be clinically feasible and it remains difficult to recruit patients in existing brain tumor trials.

In response, Technical Working Groups were informally established at the conclusion of the Brain Workshop meeting. These will be collaborative, inter-institutional groups that will focus on key technical research topics. Each group will be spearheaded by one or two researchers who will take the lead in spurring progress and collaboration and in keeping the group’s CRN page up-to-date. The following groups were established:

- **Cavitation Group** led by Arne Voie and Thilo Hoelscher at UC San Diego:
  - Members of this group will work toward the ultimate goal of controlling transcranial cavitation activity.
  - Early efforts will include developing a reliable cavitation phantom, measuring PCD signals intra- and extra-cranially, and determining methods to localize cavitation events using multiple PCDs.

- **Thermometry Group** led by Dennis Parker and Rock Hadley at the University of Utah:
  - Members of this group will work on clinically feasible (~3-second) volumetric thermometry for MRg-FUS treatments.
Early efforts will include the development of an in-water-bath “shoot-through” head coil to improve SNR with respect to body coil imaging of neurosurgical treatments.

- MR-ARFI (Acoustic Radiation Force Imaging) Group led by Kim Butts-Pauly at Stanford:
  - Members of this group will focus on optimizing skull aberration correction using this non-thermal tool
  - Early efforts will include non-thermal spot verification of CT-corrected transcranial FUS, with the emphasis shifting to the improvement of CT-corrected focus quality. The ultimate goal is to render CT correction unnecessary.

**Clinical**

- Post-workshop discussions favor opportunistic continuation of 650 KHz brain tumor trials at Toronto, Zurich, and UVa in order to prove safety and initial efficacy with the device that has been proven safe and effective for neuropathic pain and essential tremor.

- However, the consensus was that the future of brain tumor treatment (other than centrally located focal mets) will be with lower frequency transducers. There are significant technical challenges to be overcome before clinical studies can begin.

- Possibility of BBB opening with the 650KHz transducer was discussed.

- **Movement Disorders**
  - Essential Tremor
    - 15 patient trial at UVa is planned to be complete recruitment in December of 2011
    - An extension of this trial to a further 15 patients is being discussed.
    - Continue movement disorder study in Solothurn
  - Tremor Dominant Parkinson’s Disease
    - A pilot trial using the same thalamic target (VIM) as the ET pilot will be submitted in 2011.
    - An additional pilot study addressing bradykinesia/dyskinesia may follow.
    - Continue movement disorder study in Solothurn
  - Obsessive Compulsive Disorder
    - There is interest in pursuing a pilot OCD trial at YUMC in Seoul, Korea if the treatment envelope permits on the Exablate 4000 650 KHz transducer.