Research Funding Agreement Between
The Focused Ultrasound Surgery Foundation
and
Vanderbilt University
MR Temperature Imaging Toolbox for Focused Ultrasound Neurosurgery
Final Report: June 21, 2016

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University of Virginia: Craig Meyer (Co-I)

Aim 1: *Develop an accelerated 3D EPI sequence and reconstruction for preclinical whole-brain temperature imaging.*

Completed: 3D Cartesian EPI This Aim targeted a 25x-accelerated 3D EPI sequence with whole-brain coverage. We implemented this sequence on our Philips 3T scanner. While the basic acceleration was achieved simply by reducing the FOV by 5x in the two phase-encoded dimensions of the vendor's 3D EPI sequence, we have added additional phase encoding blips in those dimensions that are incremented so that the entire k-space sampling pattern shifts each dynamic, which enables a) fully-sampled baseline acquisition, which is required for the k-space hybrid reconstruction we apply to estimate temperature maps from the data; and b) undersampling artifact "blinking" between dynamics during sonications, which enables aliasing to be further filtered out with temporally-regularized reconstruction to improve temperature accuracy (as in the Utah group's TCR method; our k-space hybrid reconstruction can also incorporate temporal regularization to leverage this acceleration mechanism). This segmented acquisition scheme differs from the vendor's conventional EPI scan which would acquire all lines in a single plane of 3D k-space before moving to the next plane. An example phantom image reconstructed from this sequence is shown in **Figure 1**. This sequence is complete, but we discovered a more compelling alternative, described next.

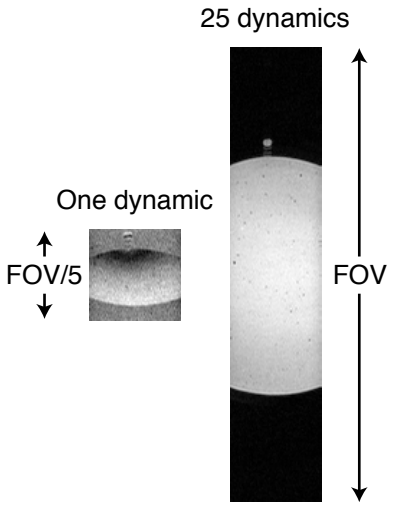

Figure 1: 3D Cartesian EPI. A *phantom image acquired using our segmented 3D EPI sequence. Left: An aliased image can be reconstructed from a single 25x/uniformly-undersampled dynamic. Right: A fully-sampled image can be reconstructed from 25 consecutive dynamics, due to the developed segmented acquisition scheme.*

Completed: 3D EPI Stack-of-Stars As a compelling alternative to conventional 3D EPI that delivers much greater volume coverage with less acceleration, we have developed a whole-brain 3D radial/stack-of-stars EPI sequence on our Philips 3T scanner, which is illustrated in **Figure 2 [11,12]**. That sequence rotates a conventional 2D EPI readout around its center in the frequency-encoded dimension, with golden angle increments. Temperature map reconstruction from data acquired using this sequence can be performed using either our k-space hybrid method **[Gaur and Grissom, MRM 2015]** or TCR, with chemical shift compensation **[3-7]** to

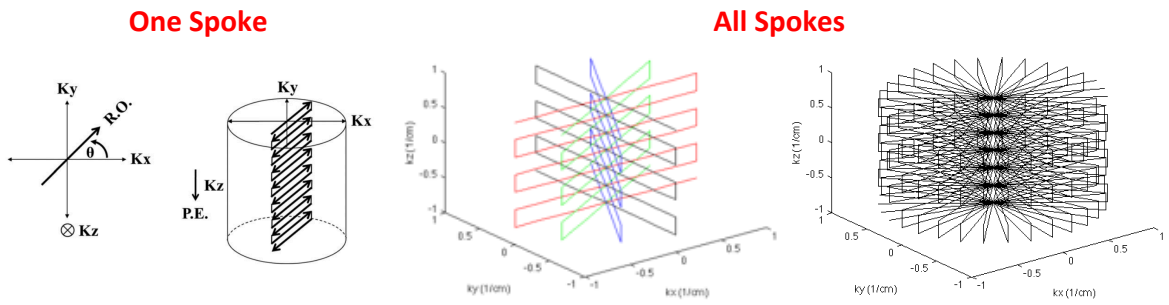

Figure 2: 3D EPI Stack-of-Stars. *Illustration of the 3D EPI stack-of-stars k-space trajectory. A 2D EPI plane/spoke is scanned each TR and rotated by 111.25 degrees between TRs to sample a 3D volume. Scan acceleration is achieved by using a small number of consecutive rotated planes/ TRs for reconstruction.*

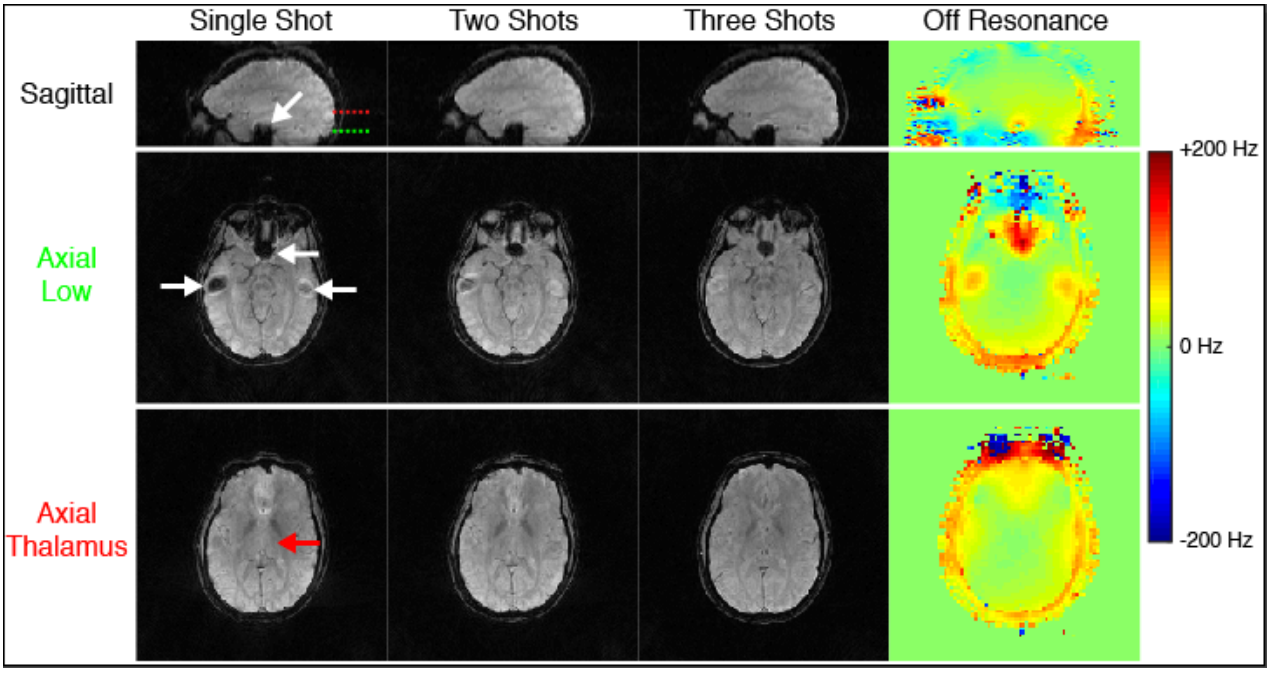

Figure 3: 3D EPI Stack-of-Stars. *Brain images acquired with the stack-of-stars EPI sequence. The sagittal and lower axial slice images contain distortions and dropout in regions with large frequency offsets (white arrows), which are diminished when multiple shots are used to shorten each readout.*

compensate any shifts that may occur with heating in the head-foot dimension; **Figure 3** shows in vivo images acquired with the sequence to illustrate volume coverage and levels of distortion, and **Figure 4** shows gel phantom sonication results using the sequence and the SonAlleve. The sequence provides artifact-free temperature maps with fine spatial resolution (1.5 x 1.5 x 2.75 mm^3) and large volume coverage (28.0 x 28.0 x 11.9 cm^3) within a 3 second frame rate when run at a modest 4.7x acceleration factor. Chemical shift blurring is negligible in the x-y dimensions but can occur in the z-dimension with this sequence; the chemical shift debarring method we describe next could be applied to alleviate blurring in z. The sequence and reconstructions are complete, and validation and publication is ongoing.

Completed: Chemical Shift Deblurring This Aim also proposed an optional chemical shift compensation step, to alleviate temperature map errors due to phase accrual across k-space

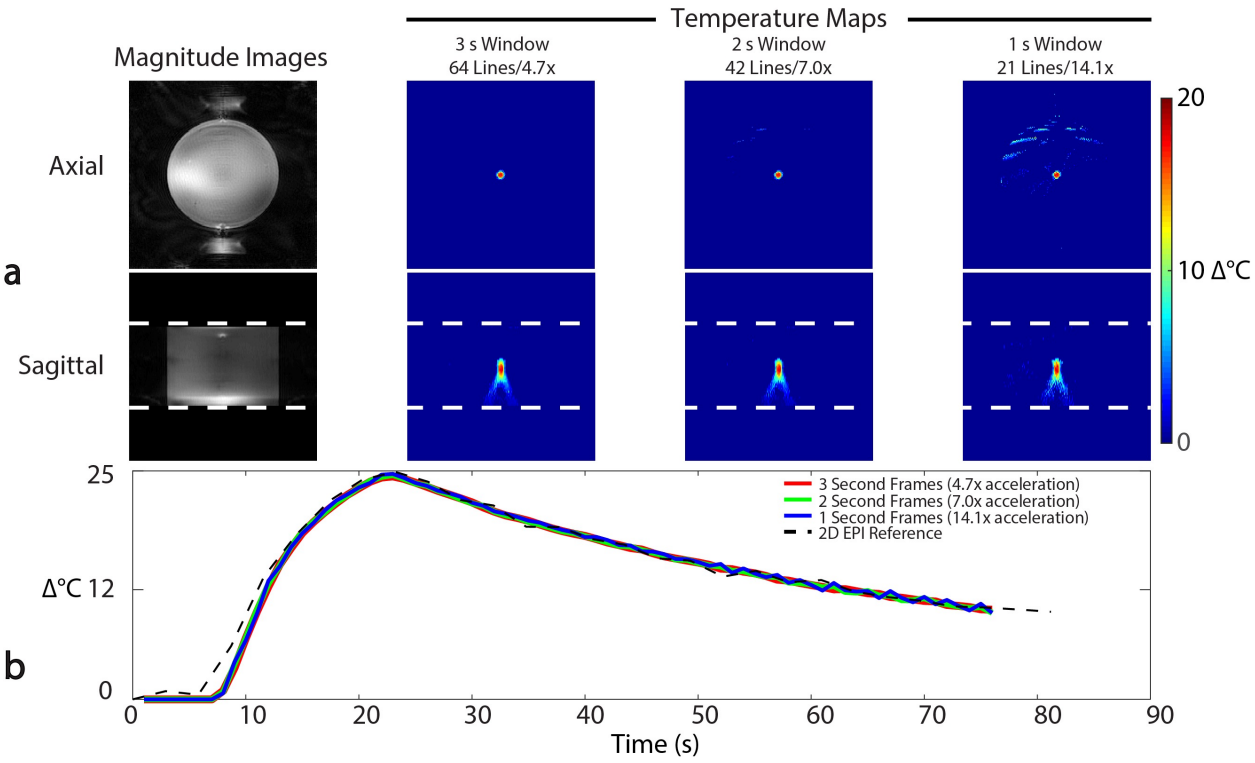

Figure 4. *Phantom temperature map reconstructions (a) and hot spot temperature curves (b) at three acceleration factors. Significant aliasing does not appear until the scan is accelerated by a factor of 14.1x, corresponding to a 1 second frame rate. There is good reference standard agreement.*

due to temperature-induced heating (i.e., the hot spot distorts itself). We completed development of that method and published it in Magnetic Resonance in Medicine **[7]**; results are shown in **Figure 5** for 2DFT and EPI temperature mapping. One unanticipated finding was that the accuracy of the reconstructions is considerably improved when we estimate both the change in chemical shift of the protons due to heating and the image attenuation due to changing T1/T2* with heat, jointly. We also developed a fast chemical shift-correction algorithm (outlined in **Figure 6**) that applies to Cartesian EPI and 2DFT data and is compatible with online use (< 0.1 s computation time for a 2D image, implemented in MATLAB without parallelization; further acceleration could be achieved with parallelized implementation). We have implemented that fast method in Python so that it can be used seamlessly in the Philips SonAlleve HIFU temperature reconstruction pipeline, and easily distributed to other sites. In May 2015 we traveled to the FUS Center at UVA to develop an RTHawk reconstruction pipeline block that implements the method. This was done with the assistance of Craig Meyer's group. The method improves the accuracy of any 2DFT or EPI temperature map acquisition, and is compatible with any temperature map estimation algorithm (e.g., baseline subtraction, referenceless, or hybrid). We also implemented L1-penalized image domain hybrid thermometry as an RTHawk block. This work is complete and published.

Ongoing: Spatially-Segmented Temperature Reconstruction We have nearly completed work to address the presence of the water bath, the signal from which is constantly changing in a

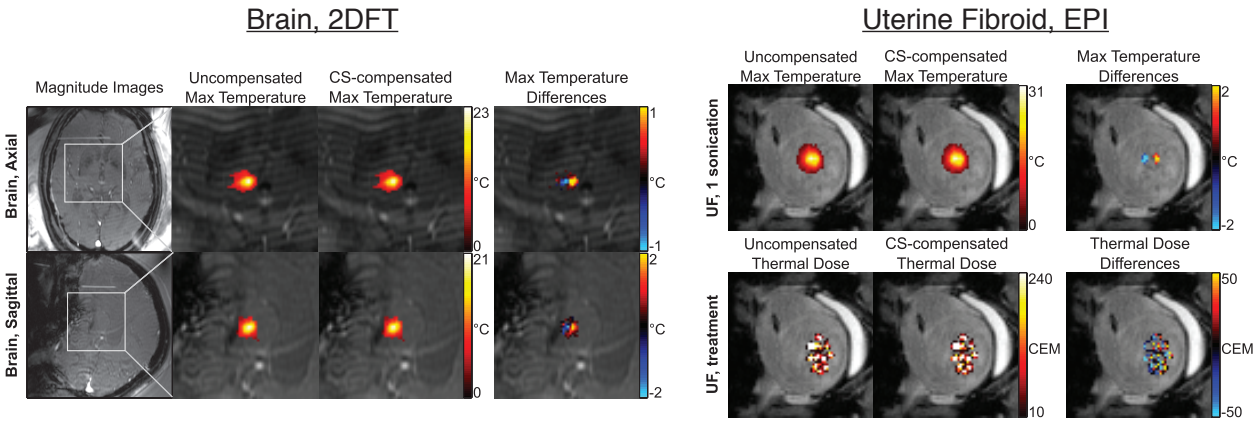

Figure 5. *Chemical shift-compensated temperature reconstruction in brain 2DFT (left) and uterine fibroid EPI MR-guided focused ultrasound procedures. In both cases, the algorithm primarily corrects a spatial shift of the hot spot and predicted necrotic regions along the chemical shift direction (left-right in both cases).*

random way, and cannot be modeled using baseline images (**Figure 7**). We have developed an spatially-segmented temperature map reconstruction approach to address this **[8-10]**. The approach works by not enforcing the hybrid image model in the water bath, but instead estimating the water bath signal using an iterative reconstruction (**Figures 8 and 9**) that is alternated with temperature recon in the brain. We have implemented and tested the method using the k-space hybrid algorithm, and are currently developing an implementation of the approach for TCR.

Ongoing Work: k-Space Hybrid Cartesian Undersampling Strategies It is not clear that uniform or even random undersampling of k-space is the best approach to accelerating Cartesian scans. Without parallel imaging, the only way to accelerate conventional scans is with partial Fourier acquisitions, which are limited to accelerations less than 2x and which have unknown effects on temperature map accuracy. We further hypothesize that uniform undersampling of k-space may result in lower temperature accuracy with k-space hybrid reconstruction than acquiring partial Fourier or even single k-space quadrants, compared to equivalently-accelerated uniform undersampling. We are currently addressing this question, the answer to which could enable larger acceleration

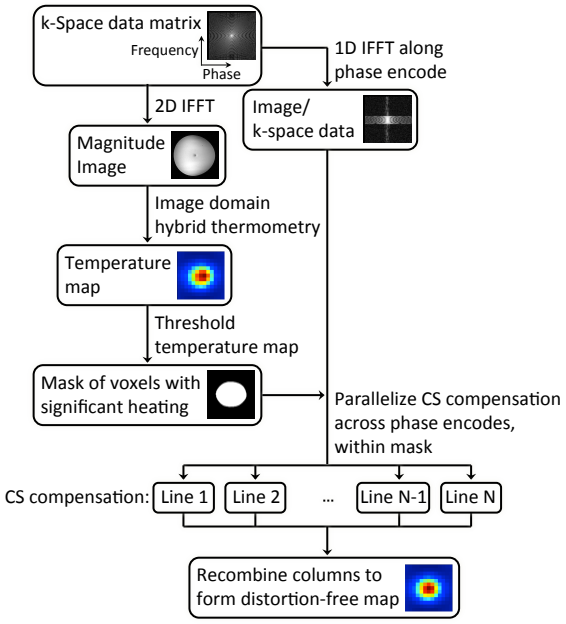

Figure 6. *Flowchart for the fast chemical shift-compensation algorithm for 2DFT and EPI scans [7]. The algorithm is implemented as a post-correction step that applies to a previously-computed temperature map. It works by iteratively correcting the temperature map to maximize consistency with the acquired k-space data. Since chemical shift blurs only in one dimension in 2DFT and EPI scans, the algorithm can be parallelized across the other dimension.*

factors with robust 2DFT and 3DFT scans than have been previously possible.

Future Work: Once work is completed on the stack-of-stars EPI sequence and temperature reconstruction, we will begin work on estimating baseline images from undersampled data without corruption by respiratory or cardiac phase and motion effects. To do this, we will treat the baseline images as additional unknowns in the temperature reconstruction, and estimate them jointly with the temperature map by enforcing a low-rank matrix constraint on the matrix of baseline images (whose rows index spatial locations and columns index temporal dynamics).

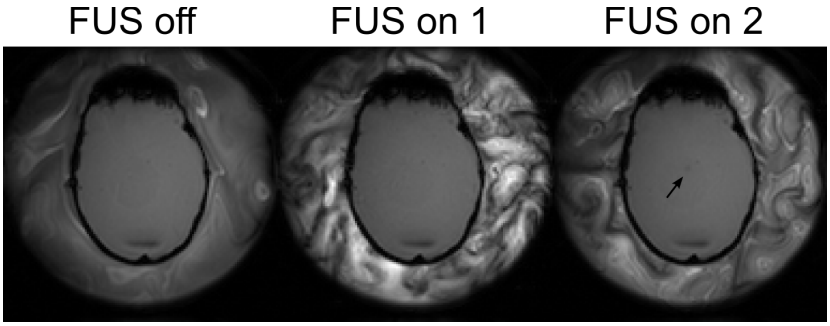

Figure 7: Spatially-segmented temperature reconstruction. *Phantom images acquired at the FUS Center with FUS off (left) and with FUS on at two different time points (middle and right). The signal in the water bath is constantly changing during sonication (hot spot indicated by arrow), so there is no baseline image available for it, and accelerated temperature map reconstructions fail since the aliased water bath energy falls into the brain.*

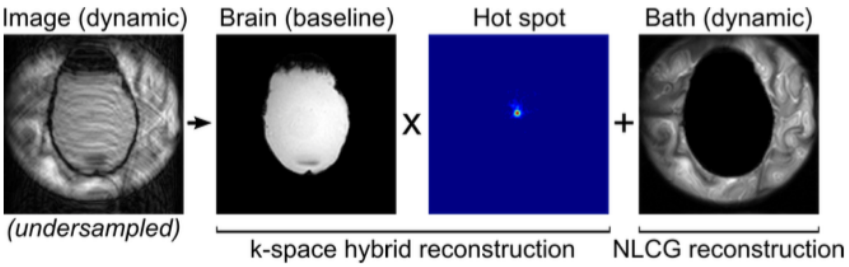

Figure 8: Spatially-segmented temperature reconstruction. *Illustration of spatially-segmented reconstruction for undersampled brain MRgFUS, which separately estimates a water bath image without a baseline, and a temperature map in the brain with a baseline.*

Aim 2: Develop an accelerated reduced-FOV 3D EPI sequence and reconstruction for test shot localization.

This Aim was not completed as originally planned. However, we believe that the EPI stack-of-stars sequence and reconstruction developed in Aim 1 fully addresses this need when acquired with a smaller slab thickness and increased resolution in the head-foot dimension.

Aim 3: *Develop a high-resolution 3D slab-selective EPI protocol and fast chemical shift-deblurring temperature reconstruction for ablation monitoring.*

As described in Aim 1, we have developed the fast chemical shift-deblurring temperature reconstruction for this Aim. Further, as for Aim 2 we believe that the EPI stack-of-stars sequence we developed for Aim 1 addresses this need when acquired with a smaller slab thickness and increased resolution in the head-foot dimension.

Presentations and Publications The following conference abstracts and papers have been published (or submitted, as indicated) on the work resulting from this project:

1. Gaur P and Grissom W A. Temperature map reconstruction directly from k-space with compensation for heating-induced geometric distortions. In: Proceedings 22nd ISMRM, 2014, p. 2362.

2. Gaur P and Grissom W A. Comparison of single and multi-echo PRF-shift thermometry and method for penalized-likelihood multi-echo temperature reconstruction. In: Proceedings 22nd ISMRM, 2014, p. 2351.
3. Gaur P and Grissom W A. Temperature map reconstruction directly from k-space with compensation for heating-induced geometric distortions. In: Proceedings ISTU 2014.
4. Gaur P and Grissom W A. Improved k-space-based MR thermometry by joint PRF phase shift and T1/T2* attenuation estimation. In: Proceedings 4th Intl Symp Foc Ultras 2014.
5. Gaur P, Werner B, Ghanouni P, Bitton R, Pauly K B, and Grissom W A. Chemical shift-compensated MR thermometry applied to brain and soft tissue tumor MR-guided focused ultrasound. In: Proceedings ISTU 2015.
6. Gaur P, Werner B, Ghanouni P, Bitton R, Pauly K B, and Grissom W A. In vivo chemical shift-compensated MR thermometry. In: Proceedings 23rd ISMRM, 2015, p. 1649.
7. Gaur P, Partanen A, Werner B, Ghanouni P, Bitton R R, Butts Pauly K B, Grissom W A. Correcting heat-induced chemical shift distortions in proton resonance frequency-shift thermometry. Magn Reson Med 76(1): 172-182, 2016.
8. P Gaur, X Feng, S Fielden, C H Meyer, B Werner, W A Grissom. Spatially-segmented undersampled temperature map reconstruction for transcranial MR-guided focused ultrasound. In Proceedings 24th Meeting of the International Society for Magnetic Resonance in Medicine, Singapore, 2016, p. 2095.

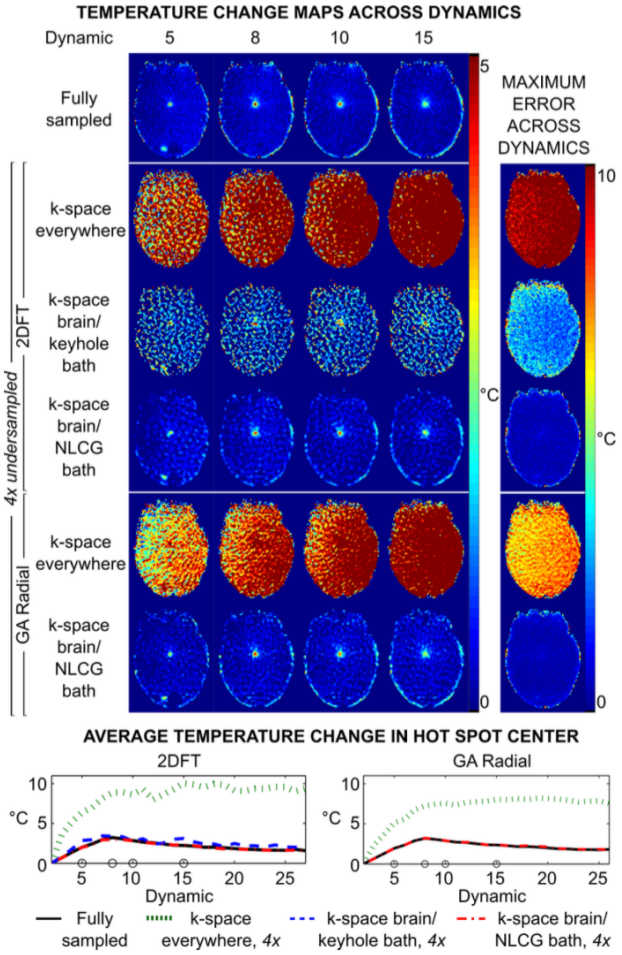

Figure 9: Spatially-segmented temperature reconstruction. *Reconstructed temperature changes and maximum temperature errors in a phantom brain sonication with 4× undersampling using 2DFT (Poisson disc) and GA radial trajectories. Fully sampled recons are compared with k-space hybrid applied to the brain and bath, k-space hybrid applied to the brain and keyhole applied to the bath, and spatially-segmented k-space hybrid (k-space brain/NLCG bath). Average temperature change over the hot spot is plotted for each reconstruction (circles on x-axis indicate dynamics of displayed maps).*

9. P Gaur, X Feng, S Fielden, C H Meyer, B Werner, W A Grissom. Spatially-segmented MRI brain and water bath reconstruction for undersampled transcranial MR-guided focused ultrasound thermometry. In Proceedings 16th International Symposium on Therapeutic Ultrasound, Tel Aviv, 2016.

10. P Gaur, X Feng, S Fielden, C H Meyer, B Werner, W A Grissom. Spatially-segmented undersampled temperature map reconstruction for transcranial MR-guided focused ultrasound. In ISMRM Workshop on Data Sampling & Image Reconstruction, 2016.
11. (SUBMITTED) S V Jonathan and W A Grissom. High Resolution Whole-Brain MR Thermometry with a 3D EPI Stack-of-Stars Pulse Sequence. Submitted to 5th Intl Symp Foc Ultras, 2016.
12. (SUBMITTED) S V Jonathan and W A Grissom. High Resolution Whole-Brain MR Thermometry with a 3D EPI Stack-of-Stars Pulse Sequence. Submitted to 11th Intl MRI Symp, 2016.

Software Developed

1. Philips R3 patch for 3D EPI. *Available on request.*
2. Philips R5 patch for 3D stack-of-stars EPI. *Available on request.*
3. Chemical shift distortion correction code for MATLAB, C, Python, and RTHawk. *Available at https://bitbucket.org/wgrissom/prf-cs-corr*
4. L1-penalized hybrid thermometry code for RTHawk. *Available at https://bitbucket.org/wgrissom/prf-cs-corr*
5. EPI Stack-of-stars k-space hybrid reconstruction code for MATLAB. *Available upon request; will be made publicly available upon manuscript submission.*

Follow-on Funding The work done under this project formed part of the preliminary data for the following grant proposals. Both of these proposals were awarded:

Title: “Curing Epilepsy With a Needle”
PI: E Barth
Grissom Role: Co-Investigator
Description: Epilepsy affects one in every 100 to 200 people globally with 50% undertreatment for surgical candidates, sudden unexplained death (SUDEP) risk of 1% per patient per year, and ineffective drug therapy for 20 to 40% of patients. This project focuses on providing access to epileptic seizure foci in the brain with a 3D-printed needle steering robot guiding a needle beneath the cheek skin and through the skull base under MRI guidance. We hypothesize that thermal therapy delivered with this needle will be less invasive and enable a greater number of patients to receive a permanent cure for epilepsy than provided by current surgical and drug therapy methods.
Sponsor: NIH/NINDS, R21
Total Award Amount (Direct + Indirect): $426,000
Dates: 6/1/2015 - 5/31/2017

Title: “Neuron selective modulation of brain circuitry in non-human primates”
PI: C F Caskey, W A Grissom, L-M Chen
Grissom Role: Co-PI
Description: An ultrasound transducer specifically designed for neurostimulation will be integrated into a high field (7T) human magnetic resonance imaging system and used to modulate the function of the well- studied visual and somatosensory systems of non-human primates. Using a mathematical model of ultrasonic interaction with neurons, we will develop acoustic pulses for transcranial stimulation that can stimulate or inhibit neuron activity. We will quantify the effects of these pulses on neural circuitry, validate the effects with neurophysiological measurements, and concurrently use functional MRI to non-invasively assess brain function at the circuit level.

Sponsor: NIH, R24 MH109105
Total Award Amount (Direct + Indirect): $1,316,458
Dates: 9/23/2015 - 6/30/2018