The Ben B. and Iris M. Margolis Foundation Imaging Symposium

November 9th, 2012

HCI Auditorium, 6th floor
2000 Circle of Hope

24nd Annual UCAIR Symposium

Program and Abstracts
Program for the 24th Annual UCAIR Symposium
November 9th, 2012
HCI Auditorium

Breakfast in the Alta View and Trailside meeting rooms (6th floor, HCI)

Introduction. Steve Stevens, MD, Chairman of the Department of Radiology

MRI: From Science to Society. Vivian Lee, MD, PhD, MBA, Senior Vice President for the Health Sciences

Presentations:
8:35 MOLECULAR AND MR IMAGING IN ONCOLOGY AND INFLAMMATION
8:35 Clinical Perspective (6 min): Introduction. John Hoffman
8:41 Rapid Multi-Tracer PET Imaging using Reduced Parameter Space Kinetic Modeling (12 min). Dan Kadrmas and M. Bugrahan Oktay
8:53 A Web-Based Resource for Lesion Detection Assessment: the Utah PET Lesion Detection Database (8 min). Alan Morey, Viktor Jiracek, and Dan J. Kadrmas
9:01 A 7-Channel Sodium and a 4-Channel Proton Breast Array for Imaging at 3T (8 min). Josh Kaggie, Rock Hadley, James Badal, John Campbell, Daniel Park, Dennis Parker, Glen Morrell, Rexford Newbould, and Neal Bangerter
9:17 18F-FDG and FLT PET for early prediction of response to targeted chemotherapy in advanced lung cancer. Zollinger, Lauren V; Morton, Kathry; Akerley, Wallace L. Kadrmas, Dan; Christian, Paul E; Butterfield, Regan; Hoffman, John M
9:25 18F-FDG PET-CT in the evaluation of acute deep venous thrombosis (12 min). Zollinger, Lauren V; Lam, Uyen; Rondina, Matthew T; Butterfield, Regan I; Beardmore, Britney; Christian, Paul E; Hoffman, John M; Morton, Kathryn
9:37 18F-FDG PET-CT in the evaluation of patients with persistent febrile neutropenia; Does PET increase reader confidence? Zollinger, Lauren V; Morton, Kathryn; Khoppula, Bhasker; Butterfield, Regan I; Beardmore, Britney; Christian, Paul E; Hoffman, John M
9:43 Clinical Perspective: Conclusions (6 min). John Hoffman

9:50 – 10:15 BREAK

10:15 HIFU (High-Intensity Focused Ultrasound)
10:15 Introduction – What do we need to know? (5 min) Allison Payne
10:20 3-D Graphical Modeling for FUS Device Design (8 min). Robb Merrill, Allison Payne, Rock Hadley, Emilee Minalga, Dennis Parker
10:36 MR sub-sampling strategies for transcranial MRgFUS applications (8 min). H. Odéen, N. Todd, M. Diakite, A. Payne, D. L. Parker
10:44 Model predictive filtering (8 min). Nick Todd, J. de Bever, S. Almquist, H. Odeen, A. Payne, D. Christensen, D. Parker
10:50 Conclusions (6 min). Allison Payne

11:00 VASCULAR IMAGING
11:00 Introduction (6min). Jennifer Majersik
11:06 Vascular Imaging (12min). Scott McNally
11:18  New MRI techniques for Atherosclerotic Plaque (8 min).  Seong-Eun Kim, Scott McNally, John Roberts, Jason Mendes, Gerald Treiman, Dennis L Parker

11:26  ASL of muscle (perfusion studies) (8 min).  Jason Mendes

11:34  Quantify tissue pO2 with BOLD MRI and modeling 12 min.  Lei Zhang, Glen Morrell, Chris Hanrahan, Alfred Cheung, Vivian S. Lee


11:58  Conclusions (6 min).  Jennifer Majersik

12:05 – 1:30 LUNCH

1:30  CARDIAC IMAGING

1:30  Introduction (6 min).  Chris McGann

1:36  Current trends in cardiac MRI (12 min).  Edward DiBella

1:48  Deformable registration for improved constrained reconstruction of ungated cardiac perfusion MRI (8 min).  Ganesh Adluru, Edward V.R. DiBella

1:56  Quantifying cardiac perfusion in patients with arrrhythmias (8 min).  Devavrat Likhite, Ganesh Adluru, Edward V.R. DiBella

2:04  Non-iterative reconstruction with a prior for undersampled radial MRI data (12 min).  Larry Zeng

2:16  Impact of Projection Truncation and a Small Number of Views on Image Reconstruction (8 min).  Yanfei Mao


2:36  Toward the development of an expandable catheter RF coil for real-time cardiac lesion MR temperature imaging (8 min).  Nelly A. Volland, R. Merrill, J. R. Hadley, E. G. Kholmovski, D. L. Parker

2:44  Conclusions (6 min).  Chris McGann

2:50 – 3:15 BREAK

3:15  NEUROIMAGING

3:15  Introduction (5 min).  Karen Salzman

3:20  Functional Connectivity MRI Classification in Autism (8 min).  Jared Nielsen, Michael Ferguson, Jeffrey Anderson

3:28  Personalized neuroscience: toward single-subject approaches for functional data (8 min).  Michael Ferguson

3:36  Simultaneous Acquisition of Dual-Nuclear MR (dnMR) Spectroscopy: 31P and 1H MRS (12 min).  Eun-Kee Jeong, Nabraj Sapkota, Josh Kaggie, Xianfeng Shi


4:04  Neurochemical Alterations in Adolescent Chronic Marijuana Smokers (12 min).  Andrew Prescott, Perry F. Renshaw, Deborah E. Yurgelun-Todd

4:16  PNS Safety of the Composite Gradient System (8 min).  Craig Goodrich

4:24  Advances in x-ray computed tomography.  (12 min).  Frederic Noo

4:36  Conclusions (6 min).  Karen Salzman

4:42  Closing remarks.  Dennis Parker
Abstract} Rapid multi-tracer PET is a technique where 2-3 PET tracers are imaged in a single scan. Using dynamic imaging with staggered injections, the imaging signals from each tracer can be estimated through application of appropriate kinetic constraints. Perhaps the most robust multi-tracer PET signal-separation algorithms rely upon parallel compartment modeling in order to estimate the signal contributions from all tracers simultaneously. As with single-tracer compartment modeling, multi-tracer modeling involves multi-dimensional nonlinear fits; however, the presence of 2-3 tracers increases the number of unknowns, introduces numerous local minima, and results in a complex fitting challenge. We previously proposed the Reduced Parameter Space Reformulation for single-tracer compartment modeling, which maximally separates the linear and nonlinear parameters of the models to facilitate application of separable nonlinear least squares techniques to reduce the problem to its simplest nonlinear form. The Reduced Parameter Space Reformulation reduces the “2K” model (1 tissue compartment with \( f_B, K_1-k_2 \)) to a single free nonlinear parameter; likewise, “3K” and “4K” models are reduced from 4 to 1 and 5 to 2 free parameters, respectively. In this work we extend the Reduced Parameter Space Reformulation to generalized multi-tracer compartment modeling, implement it in C, and evaluate multi-tracer fitting performance as compared to conventional multi-tracer modeling techniques. The reduced dimensionality of the approach makes exhaustive search algorithms feasible, which completely sample the full solution space to ensure identification of the true global minimum without fail. The proposed technique is shown to outperform iterative minimization algorithms for multi-tracer compartment modeling, avoiding issues related to convergence or trapping in local minima, and provides very robust multi-tracer model fits for rapid multi-tracer PET imaging studies.

Overview} We previously proposed a reformulation of single-tracer compartment modeling equations for 1-3 tissue compartments and 2-5 rate parameters which we call the Reduced Parameter Space Reformulation [1-2]. The reformulation maximally separates the linear and nonlinear parameters of the models, and facilitates application of the separable nonlinear least squares technique to effectively constrain the solution space to include only solutions that are least-squares in the linear sense. This approach effectively reduces the dimensionality of the nonlinear fitting problem to the smallest mathematically-identical nonlinear sub-problem, which greatly simplifies the fit. The Reduced Parameter Space Reformulation reduces the 2K model fitting problem (1 tissue compartment with \( f_B, K_1, k_2 \)) to a single free nonlinear parameter (\( u_1 \)) [1-2]. Similarly, the 3K model is reduced from 4 to 1 free parameters (\( \{f_B, K_1-k_2 \} \rightarrow u_1 \)) and the 4K model is reduced from 5 to 2 free parameters (\( \{f_B, K_1-k_2 \} \rightarrow \{u_1, u_2 \} \)). This new compartment modeling approach has been shown to provide very fast and robust single-tracer compartment model fits, even so far as enabling exhaustive search algorithms to be performed in as little as 0.01 sec. to guarantee identification of the true global minimum. Exhaustive search, which samples all possible solutions to user-defined precision, is the only nonlinear fitting algorithm that is guaranteed to identify the true global minimum in all cases; however, in general it is computationally prohibitive. The reduced dimensionality offered by the proposed Reduced Parameter Space Reformulation makes exhaustive search feasible (and indeed rapid for many compartment models).

These benefits are of even greater value for multi-tracer compartment model fitting, where the reduced dimensionality brings even greater returns. For example, conventional dual-tracer 3K+3K modeling involves a 7-dimensional nonlinear fitting problem (\( f_B \) plus \( K_1-k_1 \) for each tracer)—very difficult to fit robustly in the presence of high statistical noise; this is reduced to only 2-dimensions through application of the Reduced Parameter Space Reformulation, making the fit both simple and robust by enabling exhaustive searches to be quickly performed. In this work we extend the Reduced Parameter Space Reformulation for generalized multi-tracer compartment modeling, implement it in C, and evaluate multi-tracer fitting performance as compared to conventional multi-tracer modeling techniques.

Results} The figure below shows an example dual-tracer objective function (left) with both conventional parallel compartment modeling and with the proposed Multi-Tracer Reduced Parameter Space Reformulation. The conventional fit was performed using \( 10^8 \) iterations of simulated-annealing, which provides a means for escaping local minima and iterates toward the true global minimum provided enough iterations are performed. Both fits produced identical WSSEs and rate parameters to 4 significant digits; however, the conventional fit with simulated annealing required 32 min. whereas the proposed fit took 19.2 sec. We conclude that the proposed Reduced Parameter Space Reformulation provides very fast and robust fits for multi-tracer compartment models, overcoming the limitations of conventional compartment fitting techniques.
A Web-Based Resource for Lesion Detection Assessment: The Utah PET Lesion Detection Database
A. Michael Morey, Viktor Jiracek, and Dan J. Kadrmas

Abstract Task-based assessment of image quality is a challenging but necessary step in evaluating advancements in new PET technologies and algorithms. This work describes a collaborative resource of experimental phantom data and associated lesion-detection assessment tools that has been developed to facilitate lesion detection studies for the evaluation of PET reconstruction algorithms and related developments. The database includes 6 experimental series of custom built whole-body phantoms, including scanners from two manufacturers, with BGO and LSO crystals, operated in 2D and fully-3D modes, and with one dataset including time-of-flight measurements. The whole-body lesion detection phantoms include brain, thorax (lungs, liver, and soft tissue), and pelvis (bladder and soft tissue) compartments, each filled with F-18 activity concentrations to mimic oncologic PET imaging with F-18-fluorodeoxyglucose. Each experimental series includes 3-4 days of scanning with 4-6 sequential scans per day, providing 12-24 whole-body scans. For each set, one day of scanning had no lesions present in order to provide lesion-absent images, and the other days had 16-26 “shell-less” Ge-68 lesions (6-16mm diam.) distributed in different locations throughout the thorax and pelvis. All raw data, normalizations, and calibrations were collected and stored to the database, enabling subsequent retrospective offline reconstruction with research software for various applications. The offloaded data are further processed to identify the true lesion locations in preparation for use with both human observers and numerical studies using the channelized non-prewhitened observer, and double-blinded studies can be performed. Interested researchers are encouraged to contact the authors regarding potential collaboration and application of database experiments to their projects.

INTRODUCTION The web-based resource includes 8 series of multi-day experiments with anthropomorphic lesion-detection phantoms, coupled with analysis and processing tools for both human and numerical observer studies using localization receiver operating characteristic (LROC) analysis. Each set of experiments contains numerous lesion-present and lesion-absent image slices with known truth at 4-6 lesion contrasts. The raw coincidence data, including all normalizations and calibrations necessary for offline reconstruction by research software, are offloaded into the database for subsequent use. The database is intended for multiple retrospective studies investigating the effect of new developments in PET processing algorithms upon the lesion detection task. The data are acquired under multiple configurations using medium and large phantoms, and include datasets acquired in 2D, 3D, and 3D+time-of-flight (TOF) modes. The database, a description of new developments, and a summary of ongoing studies demonstrating the potential applications of the data.

Table I. Experimental Datasets Included in Database

<table>
<thead>
<tr>
<th>Scanner</th>
<th>Medium Phantom</th>
<th>Large Phantom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advance BGO PET (General Electric)</td>
<td>2D</td>
<td>X</td>
</tr>
<tr>
<td>Discovery ST PET/CT (General Electric)</td>
<td>N/A</td>
<td>X</td>
</tr>
<tr>
<td>Biograph TruePoint with TrueV TOF PET/CT (Siemens)</td>
<td>N/A</td>
<td>X</td>
</tr>
<tr>
<td>Biograph mCT TOF PET/CT (Siemens)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
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</table>

Database URL: http://www.ucair.med.utah.edu/FacultyKadrmas/LesDetDB_Pages/index_LDDB.html
A 7-Channel Sodium and 4-Channel Proton Array for Breast Imaging at 3T
Joshua Kaggie, Rock Hadley, James Badal, John Campbell, Daniel Park, Dennis Parker, Glen Morrell, Rexford Newbould, and Neal Bangerter

INTRODUCTION: Cancer is responsible for a quarter of all deaths in the United States (1). Breast cancer is estimated to include 29% of all new cancer cases in women in the United States during 2012, resulting in 14% of cancer related deaths (1). Early detection and improved treatment have increased breast cancer survival rates in the United States over the past two decades (1). While proton (1H) MRI is used for cancer detection due to its improved sensitivity when compared to mammography and ultrasound, 1H-MRI suffers from intermediate specificity which can result in false positive studies leading to unnecessary interventions (2). Because sodium (23Na) concentration is known to increase in malignant lesions when compared to surrounding healthy tissues (3), 23Na-MRI may be able to increase specificity, potentially improving evaluation and assessment of breast lesions (4).

Phased array coils can improve the SNR of 23Na-MRI. Phased arrays use multiple surface coils to obtain high SNR, due to the surface coils’ close proximity to the imaged sample or subject and each coil’s limited noise volume. We present a new dual resonant breast coil design consisting of a 7-channel 23Na receive array, a larger 23Na transmit cylinder, and a 4-channel 1H transceive array. Novel decoupling methods are employed for both the receive and transmit loops. This work compares the performance of our new array design to that of a coil used in prior studies consisting of a 1H and a 23Na loop and a 23Na loop containing decoupling traps. Comparisons were performed both in a phantom and in vivo. The new design achieves excellent 23Na-SNR over the sensitive volume (ranging from 2 to 5 times that of the trap design) at high resolutions (1.25x1.25x4mm in vivo) in reasonable scan times (20 minutes), while also providing good image quality for conventional 1H imaging.

METHODS:
Phased Array (Fig. 1A):
23Na Receive Loops: Six circular receive loops with 65mm diameters surround a single 75mm diameter loop on a fiberglass hemispherical former (Fig. 2). The loops were positioned using standard overlap techniques [5]. No 1H decoupling was implemented.

23Na Transmit Coil: The 23Na transmit coil consisted of 5 copper loops connected at their capacitors so that it behaved similar to a single-turn solenoid coil (Fig. 2C).

1H Transceive Loops: Four 65 mm diameter 1H loops were superimposed and offset from the 23Na loops to reduce coupling between the loops (Fig. 2A).

Trap Coil (Fig. 1B): For comparison purposes, a coil that consisted of a single transmit/receive 1H loop and a single transmit/receive 23Na loop. The 1H and 23Na loops were decoupled using traps. This coil was also placed over a fiberglass hemispherical former.

Studies: To image 23Na in a NaCl/CuSO4 phantom and the breast of a normal volunteer, we used a fast-gradient spoiled sequence using the 3D cones k-space trajectory [6] on a Siemens Trio 3T scanner. Phantom scan parameters were: TR/TE = 50/0.27 ms, flip angle = 70°, voxel size = 2.5x2.5x2.5 mm, FOV = 22.5 cm, averages = 75, scan time = ~1.5 hours. In vivo scan parameters were: TR/TE = 40/0.27 ms, flip angle = 70º, voxel size = 1.25x2x4 mm, FOV = 20 cm, averages = 20, scan time = ~20 minutes. A standard GRE hydrogen acquisition was also performed at 3 echo times, and a 3-point Dixon reconstruction was used to generate fat and water fraction images.

RESULTS:
23Na Performance: In phantom studies, the 23Na-SNR demonstrated a 2-5x increase (Fig. 3), with a mean SNR of 241±93 for the phased array and 69±16 for the trap coil within the hemispherical volume of the breast former. Similar results were observed in vivo, with the phased array displaying a 3 – 4.2x increase in 23Na-SNR over the trap coil. Improved 23Na-SNR is evident in these images with noticeably improved depiction of small anatomic features within the breast (Fig. 4A,D).

1H Performance: The 1H-SNR in the new four-element array had a mean 1H-SNR of 185±215 and the trap coil had a mean 1H-SNR of 198±75 within the hemispherical volume of the breast former. The phased array obtains good 1H images (Fig. 4B,C).

CONCLUSION: The in vivo sodium images show a level of detail and structure not previously achieved in sodium imaging of the breast, in a scan time of only 20 minutes. Our coil also demonstrates an array superposition technique that can improve decoupling between 1H and 23Na array coils, so that high SNR 23Na and 1H images can be obtained without repositioning the subject. High quality 23Na images of the breast may improve the specificity of breast MRI for the detection and characterization of breast cancer.

ACKNOWLEDGEMENTS: Supported by NIH grants 5K08CA112449 and R01DC011497, the Ben B. and Iris M. Margolis Foundation, the Benning Foundation, BYU Fulton College of Engineering, and Siemens Health Care AG.

18F-FDG and FLT PET for early prediction of response to targeted chemotherapy in advanced lung cancer.
Zollinger, Lauren V1,3; Morton, Kathryn1,3; Akerley, Wallace L2. Kadrmas, Dan1,3; Christian, Paul3 E; Butterfield, Regan3; Hoffman, John M1,3

1. Radiology, University of Utah, Salt Lake City, UT, United States. 2. Internal Medicine (Oncology), University of Utah, Salt Lake City, UT, United States. 3. Huntsman Cancer Institute (Molecular Imaging Program), Salt Lake City, UT, United States

Abstract withheld for copyright reasons
Imaging acute endotoxin-induced lung injury in a rat model

Zollinger LV1,3, Rodrigues RS2, Bozza FA2, Hoffman JM1,3, Morton KA1,3

1. Radiology, University of Utah, Salt Lake City, UT, United States. 2. National Institute of Science and Technology in Structural Biology and Biomaging-INBEB and Department of Radiology, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil. 3. Huntsman Cancer Institute (Molecular Imaging Program), Salt Lake City, UT, United States.

Abstract withheld for copyright reasons
18F FDG PET/CT in the evaluation of patients with persistent febrile neutropenia; Does FDG-PET increase reader confidence?

Zollinger, Lauren V1,2; Morton, Kathryn1,2; Khoppula, Bhasker1; Butterfield, Regan2; Beardmore, Britney2; Christian, Paul E2; Hoffman, John M1,2

1. Radiology, University of Utah, Salt Lake City, UT, United States. 2. Huntsman Cancer Institute (Molecular Imaging Program), Salt Lake City, UT, United States.

Abstract withheld for copyright reasons
18F-FDG PET-CT in the evaluation of acute deep venous thrombosis.
Zollinger, Lauren V.1,4; Lam, Uyen2; Rondina, Matthew T.3; Butterfield, Regan I.4; Beardmore, Britney4;
Christian, Paul E.4; Hoffman, John M1,4; Morton, Kathryn1,4

1. Radiology, University of Utah, Salt Lake City, UT, United States. 2. University of Utah School of Medicine, Salt Lake City, UT, United States. 3. Internal Medicine, University of Utah, Salt Lake City, UT, United States. 4. Huntsman Cancer Institute (Molecular Imaging Program), Salt Lake City, UT, United States.

Abstract withheld for copyright reasons
Introduction: Medical equipment laboratories are relying more and more on computer-aided design and simulation of their prototype devices in an effort to reduce hardware development costs and manage the increased complexity of modern imaging technology. MRI scanners support an ever-increasing number of advanced functions, i.e., a greater number of coil receive channels and the integration of interventional hardware. Realistic computer modeling has greatly facilitated the task of optimizing device functionality on such an ever-increasing scale of complexity.

A significant limitation to the design of complex MRI coils and integrated interventional devices has been the absence of adequate digital models of the human anatomy and scanner hardware. Mathematical programming suites such as Matlab have successfully simulated the electromagnetic, thermal, and acoustic physics of magnetic resonance guided focused ultrasound (MRgFUS) treatments and systems with relatively simple geometries. However, the mechanical layout of hardware devices relative to the human subject is very cumbersome to analyze and predict in non-graphical software packages. Modeling the organic nature of human anatomy has presented a considerable challenge to geometric design in programs with rigidly mathematical user interfaces.

Advanced 3-D design software has been used to design and construct a dedicated MRI guided breast FUS device as well as the RF coil arrays for a transcranial MRgFUS device. Because FUS treatment during scan time requires accurate temperature monitoring, the implementation of a dedicated MRI coil was of chief concern during the design process of each device to obtain maximum coil SNR and temperature accuracy. After placing a human model ‘patient’ inside an accurate scanner model, device hardware can be designed around the patient within the scanner bore to achieve maximum patient comfort and treatment region access.

Methods: Human models were created in SolidWorks 3-D modeling software for FUS brain and breast treatment. Clinical MRI scans were consulted for approximate feature location. Brain and breast treatment hardware devices were rotated through their maximum ranges of adjustability to detect mechanical interference with the patient table and scanner. “Treatable Volume” regions were obtained by sweeping the ultrasound focal region through the full range of mechanical and electronic transducer steering.

Results: Inexpensive 3-D human models were developed using SolidWorks CAD software that provided sufficient anatomical detail for relevant body parts. Hardware and coils of various sizes and configurations can be easily applied and precisely arranged relative to the models.

Discussion: Body parts of approximate location and shape were deemed sufficient for coil simulation due to variability of human anatomy. Additional time can be invested to produce finer and more accurate detail of organs, or to adjust the location and size of individual organs (e.g. depth and diameter of carotid arteries) to model treatment of non-average patients.

Acknowledgements: This work is supported by NIH grants R01 CA134599 and R01 EB013433 and the Ben B. and Iris M. Margolis Foundation.
Introduction

The purpose of this work was to design a coil that allows for open ultrasound access to the cranium for interventional MRI, provides high SNR in the brain, and keeps the majority of the coil circuitry away from the top of the head. This coil could ultimately be used in transcranial MRI guided focused ultrasound (MRgHIFU) systems.

Methods

Two coil designs were investigated. Both had coil elements that were non-overlapped and capacitively decoupled in a common leg. The first design was a triangular-shaped, three-channel phased array that fit on top of the head like a cap. The second design had 7 rectangular elements that wrapped around the back of the head. Both designs were integrated with a stereotactic head frame.

Three experiments were performed in a Siemens TIM Trio 3T MRI scanner (Erlangen, Germany). Comparisons were done with the following three coils: Body coil (BC), 11-channel (11ch) HIFU coil, and 6-channel (7ch) brain ladder coil.

Exp.1) Signal to Noise Ratio (SNR) maps were obtained using a standard gradient echo pulse sequence

Exp.2) To compare the relative temperature measurement performance of the coils, the 2D GRE sequence was repeated 39 times on a single human volunteer using the BC, 11ch and the 7ch coils. The standard deviation of the calculated temperature through time was calculated for each pixel in the image.

Exp.3) Finally, To assess the ultrasound transparency of a single coil rung of the 3ch coil, MRI temperatures were made while a single point and circular HIFU heating trajectories were performed in a homogeneous phantom with and without a single copper/kapton trace.

Results

Exp.1) The SNR plots showed that in the central brain the 11ch/7ch coils had a 185%/216% increase compared to the BC in the center of the brain and a 831%/950% in the side of the brain. 0.30 °C (0.98 °C) for the 11ch. For the 7ch the temperature error 9cm from the top of the head was 0.24°C.

Exp.3) Phantom temperature measurements made with and without the copper/kapton coil rung in place showed no significant difference in the heating patterns for the single point and circular trajectories.

Both the ladder and cap coils could be used together with the little coupling. The maximum noise coupling between any of the channels was 0.5249.

Discussion and Conclusions

Both coils gave better SNR results in the central brain region than the body coil. The 3ch cap coil gave better SNR at the cranium surface and the 7ch gave better SNR in the deep central portion of the brain. When combined together great coverage of the entire head region of interest was obtained. Both coils are designed to fit around and operate with the stereotactic head device and to not interfere with the ultrasound beam unlike many clinically available RF head coils. Both coils are a good trade off between design simplicity, compatibility with the stereotactic frame, and improved SNR in the brain. Patient treatment should be improved with the high SNR and better MR anatomy images provided by either coil. Both coils will also provide improved temperature monitoring for transcranial MRgFUS treatments.
**MR sub-sampling strategies for transcranial MRgFUS applications**

1. H. Odéen, N. Todd, M. Diakite, A. Payne, D. L. Parker

1 UCAIR, Department of Radiology 2 Department of Physics and Astronomy, Univ. of Utah, Salt Lake City, UT, USA

**Background/Introduction**

Transcranial MRgFUS requires accurate temperature measurements with high spatio-temporal resolution over the fully insonified 3D field of view (FoV) to assess treatment and monitor heating in both near-field tissue-bone interfaces and the treatment site. To achieve high spatio-temporal resolution over the large FoV many researchers utilize sub-sampling of k-space in conjunction with e.g. parallel imaging, constrained reconstruction or model based reconstruction algorithms. Here we present a comparison between three sub-sampling schemes, which are reconstructed with a constrained reconstruction method.

**Methods**

**Subsampling schemes** Three different subsampling schemes were implemented in a 3D Segmented EPI sequence on a Siemens 3T MRI scanner (Tim Trio, Siemens Healthcare AG, Erlangen, Germany). The variable density subsampling (VDSS) scheme, taking advantage of the fact that most of the energy of k-space is located in the center, applied a VDSS pattern in the phase encode-slice encode plane (k_y-k_z), while fully sampling the read out direction (k_x). The k_y-k_z plane was divided into 2D regions, where the central region was fully sampled every time, and the outer regions were sampled with increasing reduction factors (R), ranging from 3 to 13, see figure 1. The echo train was applied centrically, i.e. the center most region of k-space was sampled with the last echo in the echo train, to maximize the temperature sensitivity [1]. The second scheme fully sampled the k_x and k_z directions, while applying even subsampling (ESS) in the k_y direction. In this scheme the echo train was applied sequentially, so that the center of k-space was sampled at the center of the echo train. The third scheme (VD-ESS) applied a variable density subsampling in the k_z direction (R ranging from 3 to 16) while even subsampling in the k_y direction, and fully sampled the k_x direction. The echo train was applied as in the ESS scheme.

**Temporally Constrained Reconstruction (TCR)** In the previously described TCR algorithm [2-3] the sequence of temperature images is obtained by iteratively minimizing a cost function consisting of a constraint term and a data fidelity term using a gradient descent method.

**Experiment** HIFU heatings (100 W for 48.1 s) were performed on *ex vivo* pork muscle embedded in an agar gel phantom containing a plastic scull to mimic a human head. The three subsampling schemes were compared to a fully sampled “truth”. Imaging parameters included voxel size=2x2x3 mm^3, TR = 33 ms, TE = 12.0 (for ESS and VD-ESS) and 18.5 (for VDSS) ms, EPI factor=7, bandwidth=752 Hz/pixel, t_acq=3.7 s. For the fully sampled “truth” the imaging matrix was 128x77x10. To achieve the same reduction factor (R=7) for all three subsampling schemes the matrix size for the ESS and VD-ESS were 128x98x54, and the VDSS matrix was 128x126x44. All temperatures were calculated using the proton resonance frequency (PRF) shift method.

**Results and Conclusions**

Data acquired with the VDSS underestimates the maximum temperatures, while data acquired with the ESS and VD-ESS schemes perform well. Part of the problem with the VDSS scheme is attributed to the frequency shift due to temperature that causes a linear phase shift of opposite polarities in the upper and lower parts of k-space, and lead to a blurring of the hot spot. In the ESS and VD-ESS schemes the frequency shift causes a linear phase shift across all of k-space, leading to a small shift in the position of the hot spot (but no blurring). Further, echo shifting is hard to implement in the VDSS scheme, as it has to be done simultaneously in two directions.

**Acknowledgments**

This work was supported by The Ben B. and Iris M. Margolis Foundation, The Focused Ultrasound Surgery Foundation, Siemens Healthcare, and NIH grants F32 EB012917-02, and R01s EB013433, and CA134599.

**References**

BACKGROUND. Focusing ultrasound energy through the intact skull for transcranial MR-guided focused ultrasound surgery (MRgFUS) applications is a challenge as absorption and reflection at the bone interfaces can lead to beam attenuation and undesirable heating. Proper monitoring of skull surface heating is difficult due to the large acoustic window needed for transcranial MRgFUS. Here we present a large coverage 3D imaging method for simultaneously mapping the temperature changes over the entire skull surface and at the focal spot.

METHODS. Two sets of experiments were carried out to determine the feasibility of monitoring temperature changes over the entire skull. First, in vivo imaging of a human volunteer was performed with no heating. The tissue on the outer surface of the skull was segmented and the pixel-wise temperature standard deviation over time was calculated over the entire surface. Second, transcranial MRgFUS was done on an ex vivo human skull flap embedded in an agar mold. The agar on the outer surface of the skull was segmented and temperature maps over the entire skull flap were created.

A 3D segmented EPI sequence was used for imaging with 36 slices and a modification to allow even undersampling in the k_y direction. Sequence parameters for the in vivo imaging were: 192x88x40 imaging matrix; TR/TE = 37/11ms; 1.5x2.0x2.5mm resolution; EPI factor 11; 4X undersample factor; 3.0s per undersampled time frame. Sequence parameters for the ex vivo imaging were: 128x110x40 imaging matrix; TR/TE = 30/11ms; 2.0x2.0x2.5mm resolution; EPI factor 11; 5X undersample factor; 2.4s per undersampled time frame.

RESULTS. Full skull coverage was achieved for the in vivo imaging with the 3D volume extending 7cm into the brain. A 2D projection of the temperature standard deviation map over the skin surface is shown in Figure 1C (mean STD is 1.1 +/- 0.3C°). The sequence successfully measured temperature changes over the entire skull flap during the ex vivo MRgFUS heating experiment. A 2D projection of the temperature change over the skull flap is shown in Figure 2C. The volume coverage was large enough to simultaneously see the heating at the focal zone (not shown).

CONCLUSIONS. We have demonstrated the feasibility of measuring temperature changes over the entire skull surface during transcranial MRgFUS. The technique will be useful for pre-clinical characterization of surface heating effects and, ultimately, for improved treatment monitoring.
New MRI techniques of Atherosclerotic Plaque

Seong-Eun Kim¹,², Scott McNally², John Roberts¹,², Jason Mandes¹,², Gerald Treiman³,⁴, Dennis L Parker¹,²
¹UCAIR, ²Department of Radiology, ³Department of Surgery, University of Utah
⁴Department of Veterans Affairs, VASLCHCS, Salt Lake City, Utah

It has been reported that atherosclerosis of carotid artery is the direct cause of the ischemic stroke (1-2). Cerebral ischemic events cause by carotid plaque is mainly associated with plaque instability (3). However, current stenosis basis risk stratification is not sufficiently patient specific and could be improved if risk factors could be determined based upon plaque component along with plaque morphology measurements.

Prospective longitudinal studies using by MRI techniques which can image plaque surface morphology and composition, prospective longitudinal studies have suggested that carotid inflammation, intraplaque hemorrhage (IPH) and plaque surface disruption are associated with a higher risk of cerebral ischemic events(4-6). Although promising of MRI, the accuracy of these is limited by the small size of important plaque features, the depth of the artery, patient motion, and the general limitations of the MRI techniques used.

In carotid artery imaging projects, we have developed new acquisition and reconstruction methods to improve the detection and characterization of these plaque details, and then confirm the accuracy of these advances. New RF coil designs such as 16 channels of phased array could create increased image signal-to-noise ratio (SNR) and faster imaging (7). New acquisition and reconstruction techniques such as Cine technique combined with compress sensing algorithm designed to reduce blurring and artifacts due to physiological motions could achieve a marked increase in in-vivo spatial resolution and clarity of plaque components (8). Novel MRI techniques such as DWI, T1 and T2* measurements could provide the additional important clinical information (9-10). This increased clarity will lay the foundation for studies to determine which aspects of plaque composition or characteristics. It will also have potential advantage in a variety of diagnostic applications and will be of substantial values in clarifying carotid disease. Finally, it can better determine stroke risk from carotid atherosclerosis.

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Simultaneous Measurement of Perfusion and BOLD changes in Calf Muscle During Exercise

Jason Mendes

Target Audience
Clinicians and researchers who wish to assess the severity of peripheral arterial disease (PAD) and monitor response to therapeutic interventions designed to improve skeletal muscle perfusion.

Purpose
It has been demonstrated that measurements of perfusion and blood oxygen level dependent (BOLD) changes in skeletal muscle can improve tissue assessment in peripheral arterial disease (1,2). Recently a pulse sequence (SQUAB) was proposed to simultaneously measure quantitative perfusion maps and BOLD changes in skeletal muscle after exercise (3). However, we have demonstrated that imperfections in the saturation/inversion pulses cause significant errors in the measurement of perfusion. This work demonstrates the feasibility of a modified version of SQUAB which accounts for imperfect saturation/inversion pulses in the measurement of perfusion. The modified sequence was applied in volunteer studies with a graded exercise routine.

Method
The modified saturation inversion recovery sequence block shown in Figure 1 was repeated every 5 seconds during the experiments. The inversion time was 0.8s, leaving about 3 seconds to exercise every repetition interval (TR). During each three second exercise window, the volunteer was asked to plantar flex three times with a specified weight load. This method of interleaved exercise and imaging allowed for an adequate buildup of muscle perfusion while still allowing measurements to be made during the exercise phase itself rather than just during the recovery. Each experiment began with 1 minute of baseline measurements where the volunteer did not exercise during each 3 second exercise window. This was followed by three minutes of exercise and two minutes of recovery (no exercise) interleaved with imaging. Four separate experiments were conducted with varying amounts of weight for exercise (typically 4, 8, 12 and 16 pounds) each separated by an additional 5 minutes of rest to allow perfusion to return to baseline.

All studies were performed on a Siemens Trio 3T MRI scanner with a 4 element flex coil. All human studies were approved by the institutional review board and informed consent was obtained from all subjects. Dual echo EPI images were acquired at TE=23/58ms, FOV=160mmx160mmx10mm, 64x64 pixels, a 7-lobe Sinc slice selective saturation pulse and 3 composite pulses (90°-180°-90°) for the non-selective inversion.

Results and Discussion
The first set of EPI images are used in the calculation of T2* and to correct for changes in $M_0$ during the experiment. The second and third set of EPI images are used in the calculation of perfusion. Figure 2 shows the perfusion maps for an axial slice through the calf before and after exercise. Figure 3 and 4 show the perfusion and T2* changes during exercise and recovery. A graded increase in perfusion is observed during exercise as well as a decrease in T2* due to the increased deoxygenated blood.

Conclusion
Simultaneous measurements of both perfusion and BOLD changes can be successfully interleaved with an exercise protocol.

References
Quantify renal tissue pO₂ with BOLD MRI and modeling
Jeff L. Zhang, Glen Morrell, Chris Hanrahan, Alfred Cheung, Vivian S. Lee
Departments of Radiology and Nephrology, University of Utah

Background: Despite high blood flow to the kidney, renal medulla works in a hypoxic state, in part because of the high metabolic activity in medulla and in part because of artero-venous shunting. Variation in oxygen saturation in renal medulla plays a critical role in renal pathologies. Blood Oxygen Level Dependent (BOLD) MRI is a technique where tissue signal reflects the paramagnetic property of unoxygcnated hemoglobin molecules. $R_2^*$, estimated from BOLD acquisitions has been found to be a good surrogate for tissue oxygenation. However, multiple factors including tissue vascular fraction and water diffusion rate may contribute to $R_2^*$. These factors are particularly relevant in the kidneys and need to be studied for renal BOLD application.

Our studies and recent findings: We developed a Monte Carlo simulation approach for analyzing renal BOLD signals using parameters specific to the kidney, and an oxygen transit model for exploring the transit of oxygen among the various compartments in kidney tissue. With the two models, we are able to estimate tissue pO₂ (with unit mmHg) from BOLD data. In this symposium, we will present our recent work on the models:

(1) Quantify the contribution of each individual confounding factor in BOLD signals: we know that, besides deoxyhemoglobin, multiple other factors could affect renal BOLD signals. It is desirable to know the relative contribution from these factors for two reasons: a) this helps interpret BOLD signals in some renal diseases that some factors change; b) in model simplification for improving robustness, the factors with large contribution and large variation will need to be measured in vivo while those with little contribution or variation can be safely assumed. We performed a sensitivity analysis by varying the parameter of interest in its typical range and running the Monte Carlo simulation. We found that that both vascular fraction and capillary hematocrit are positively linear to renal $R_{2p}$, an increase of the radius of blood vessels up to about 10 µm led to an increase of $R_{2p}$, and coefficient of water diffusion inside or outside of vascular space did not affect BOLD signals. Based on the results, we obtained a linear regression formula for renal medulla,

$$R_{2p} = -22.5 + (1 + 10.1 \cdot v_a) \cdot (1 + 10.1 \cdot Hct) \cdot [1 + 5.6 \cdot (1 - SHb)] + 1.1 \cdot R_a$$

[1a]

$$R_{2p} = -3.0 + 1197.6 \cdot v_a \cdot Hct \cdot (1 - SHb)$$

[1b]

These formulas could help us determine SHb from $R_{2p}$ in a quicker way than complicated simulation.

(2) Interpret complicated relationship among oxygen delivery, oxygen consumption and BOLD signals, using our proposed oxygen transit model. Researchers have applied BOLD in many renal diseases and have been trying to figure out the possible changes in oxygen delivery and/or consumption rates with the diseases based on the BOLD signals. Besides its use for estimating tissue pO₂, our model provides a quantitative tool for explore the above-mentioned relationships. In this study, we varied those delivery-related parameters and those consumption related parameters, and monitored the change in model-estimated tissue pO₂ and BOLD signals.

Our BOLD study with skeletal muscle: Muscle has unique features in oxygen consumption and a non-invasive technique for oxygenation assessment, like BOLD, is desirable. We are adapting our BOLD model for skeletal muscle, and will present our progress and the challenges we met.
Introduction: Renal hypoxia is thought to be a major factor in the development of chronic kidney disease (CKD) and end stage renal disease. Renal BOLD imaging is a method of measuring renal hypoxia by estimating $T2^*$. Published renal BOLD data is somewhat ambiguous and contradictory, possibly due to limitations in the underlying MR imaging. Because the kidneys move with respiration, published renal BOLD data has been limited to multi echo GRE performed during a single breath hold, which gives poor resolution and signal to noise ratio (SNR). We have implemented a multi echo GRE sequence with prospective navigation which allows motion artifact-free imaging over an arbitrarily long period of free breathing. Image time can be flexibly traded off for resolution and SNR. This method gives $T2^*$ maps of the kidneys with excellent resolution and SNR.

Methods: The prospectively navigated sequence is shown in Figure 1. The sequence runs with constant sequence repetition time (TR). A one-dimensional navigator echo is acquired at the beginning of each TR, typically prescribed in a sagittal plane intersecting the right hemidiaphragm. Navigators are used to define "bins" corresponding to different points in the respiratory cycle. A separate k-space is accumulated for each navigator bin. Navigators are analyzed in real-time immediately after being acquired. Each new navigator is compared to the navigators defining existing bins. If the new navigator is sufficiently similar to the navigator defining an existing k-space bin, the data from the current TR is assigned to that k-space bin. If the new navigator is not sufficiently similar to any of the navigators defining existing bins, it defines a new bin. The selected bin is examined to see what k-space line should be acquired next for that bin, and this phase-encode step is fed back in real-time to the running sequence, which then acquires that phase encode step. The sequence finishes when one bin has a full k-space. A set of motion-free images with different echo times is reconstructed from the full k-space bin. $T2^*$ estimation is performed by non-linear fitting of signal intensity from images of 12 different echo times to a monoexponential decay for each pixel.

Results: Figure 2 shows a renal $T2^*$ map formed from a conventional 20 second breath-hold scan (panel A) and $T2^*$ map formed with the new sequence with a 10 minute free-breathing prospectively navigated sequence, 10 minute imaging time. Scale is in milliseconds.

Discussion: Prospective navigation with real-time feedback has been used to reduce motion artifact, mostly in cardiac imaging (1-4). This technique has not been previously applied to a specific abdominal imaging scenario such as renal BOLD imaging. The free tradeoff of imaging time for resolution and SNR possible with our sequence gives renal BOLD $T2^*$ maps of unprecedented resolution and SNR, which will help to better evaluate renal BOLD as a potential tool to follow the course of CKD.

Deformable registration for improved constrained reconstruction of ungated cardiac perfusion MRI

Ganesh Adluru, Edward V.R. DiBella

Introduction: Ungated cardiac perfusion imaging is a recently proposed approach to image patients with cardiac arrhythmias [1]. The method can be efficient in continuously acquiring multiple slices by ignoring missed triggers and can be an easier alternative to the standard gated acquisitions in terms of patient setup and obtaining good gating signal at high field strengths. However more advanced reconstruction and processing methods are required to make such an acquisition clinically useful. It was shown that an undersampled radial acquisition with a spatio-temporal constrained reconstruction (STCR) gave good quality images that were clinically diagnostic [2,3]. The reconstruction method was fairly robust to some amount of cardiac as well as respiratory motion. However when severe cardiac and respiratory inter-frame motion is present it is common in stress perfusion imaging, spatial and temporal blurring may be inevitable. Here we propose a reconstruction framework to improve the image quality in such cases by incorporating motion information into the reconstruction. Methods have been proposed to fold in motion estimation into compressed sensing reconstruction to reduce blurring from inter-frame motion in dynamic imaging [4-6]. Ungated perfusion imaging is more challenging as the contrast in the images is changing in addition to cardiac and respiratory motion. Here we use a model-based diffeomorphic image registration that can handle contrast variation in the images in conjunction with a self-gating method that can lead improved reconstructions.

Methods: Undersampled radial cardiac perfusion data ignoring ECG gating and at pharmacologically induced stress was acquired on a Siemens 3T Verio scanner using a saturation recovery pulse sequence. Golden ratio based angle spacing of 111.25° was used between the rays. Scan parameters were TR = 2.2 ms, TE = 1.3 ms, matrix size = 288 x 24, [Gd] = 0.075 mmol/kg. Four slices and 250 time frames were acquired. A preliminary STCR reconstruction with total variation constraints [7] as shown in (1) was performed using all of the acquired data to reduce streaking and errors in the motion estimation process. In (1), E incorporates undersampling pattern and coil-sensitivities information that are estimated by using the last 360 spokes in the acquisition. \(TV_r\) and \(TV_i\) represent total variation constraints [8] along time and space respectively with weights \(\alpha_r\) and \(\alpha_i\). \(d\) is the acquired k-space data, \(m\) the reconstructed complex image estimate.

\[
\min_{m} \|E(m) - d\|^2 + \alpha_r TV_r(m) + \alpha_i TV_i(m) \quad (1)
\]

Self-gating was performed using magnitude images obtained from (1) as described in [1,3] to identify cardiac motion. A region of interest around the heart was automatically found and signal intensities in the ROI were summed to obtain a self-gating signal. The image series were binned into (i) approximate systole and (ii) approximate diastole by finding troughs and peaks in the signal. In order to estimate residual cardiac and respiratory motion within each bin we compute diffeomorphic deformation maps using a model-based approach similar to the one proposed in [9]. Model reference images were generated by using a two-compartmental model with an input from a region of interest in the RV blood pool [10]. Each image was registered to its corresponding model reference image to obtain a deformation map. We used Advanced Normalization ToolS (ANTS) diffeomorphic registration tool [11], built using ITK [12]. The method was originally developed and used in the context of neuroimaging and it gave favorable results compared to several existing state-of-the-art registration methods [13]. The method uses a cross-correlation cost function with symmetric normalization transformation of images and with a Gaussian regularizer on the velocity fields as described in [14]. A major advantage of the symmetric diffeomorphic registration approach is that an inverse deformation map exists and also it can handle both large as well as small deformations. The computed deformation maps were also updated every iteration of the minimization. The pipeline of the proposed framework is summarized in Figure 1.

Discussion: Estimating and applying diffeomorphic maps every iteration increases computational burden in the proposed multi-coil STCR reconstruction. Parallel computing using 12 CPU cores resulted in additional 14 minutes per iteration. Using GPUs can reduce this additional burden. The proposed framework results in deformation maps that can be used to suppress motion to compute quantitative perfusion parameters. Proposed self-gating with deformable registration can be a promising framework to improve image quality of cardiac perfusion MRI with inter-frame motion.

Quantifying cardiac perfusion in patients with arrhythmia

Devavrat Likhite¹, Ganesh Adluru¹, Edward V.R. DiBella¹
¹UCAIR, Department of Radiology, University of Utah

Introduction: Dynamic contrast enhanced (DCE) MRI is maturing as a tool to quantify myocardial blood flow. The general approach is to acquire multiple imaging planes through the heart and track the uptake and washout of the contrast agent through the chambers into the myocardium. Generally an ECG–gated sequence is used to acquire 4-5 short axis slices spanning the heart from the base to the apex. However, this creates a problem in patients with arrhythmia wherein the irregular heartbeats lead to missed triggers. And at high field strengths, gating becomes a problem. Recently a new concept of ungated acquisition and retrospective self-gating was introduced [1]. Here we compare ungated perfusion acquisition directly with gated acquisition to determine the effectiveness of ungated acquisition in the estimation of myocardial blood flow.

Methods: Cardiac perfusion data was acquired using a saturation recovery turboFLASH sequence in 7 volunteers in sinus rhythm (male/female) at rest. The acquisition parameters were TR=2.2ms, TE=1.2ms on a 3T Verio (Siemens) scanner. Four to five slices were acquired with a delay of ~50ms, gadoteridol 0.05mmol/kg was injected and ~230 slices were acquired over the duration of a minute with no gating and breath hold or shallow breathing. The same sequence was used with gating. Prior to the ungated and gated acquisitions, dilute (10%) volume matched acquisitions were performed to get the unsaturated AIFs [2].

Images were reconstructed using a spatio-temporally constrained reconstruction (STCR) method [3]. The initial step of self-gating [1] involved automatic localization of the LV and RV and summing the signal intensity around the RV to cluster the timeframe into systolic or diastolic based on a peak or a trough. Figure 1 shows the effectiveness of the automatic algorithm in finding the location of right and the left ventricle (RV and LV). Figure 2 shows the plot of the sum in the region and the corresponding location of peaks and troughs classified as systolic and diastolic timeframes. The binned images still have some motion in them as they are not acquired during the same cardiac phase. Figure 3 shows the images binned into systole and diastole for two datasets. Deformable registration is employed to suppress the cardiac motion. Further processing involves automatic image segmentation with manual adjustments and extraction of the 6 azimuthal region blood curves per slice. The precontrast value was subtracted off from each tissue curve. Manual rigid shifts were performed in some datasets to account for breathing motion. The AIF was provided from a low dose diastolic slice scaled by a factor of 10. The data was fit to a two compartment model and the $K_{trans}$ was reported. The same processing steps except the initial self–gating were performed on the gated datasets to report the $K_{trans}$.

Results: Here we have compared the perfusion indices that we obtain from our ungated method to those obtained using gated acquisition. Figure 4 compares the perfusion values obtained from gated acquisition on the x axis versus those obtained from self-gated (diastole) on the y axis. The different datasets are color coded. From the plot it is seen that there is a coefficient of correlation of 0.8 between the gated and self-gated (diastole) acquisition.

Discussions: Here we have compared our self-gated approach to the gated acquisition for the evaluation of perfusion parameters. The results show that there is a decent match between self-gated and gated thereby paving way for the further development of ungated acquisition.

Developments in area of segmentation, registration show a promising future for self-gated acquisition in the estimation of perfusion parameters in patients with arrhythmia and in acquisitions at high field strength where ECG gating becomes a problem.

This paper gives a rigorous derivation of the FBP-MAP (Filtered Backprojection Maximum a Posteriori) algorithm, which was suggested in an ad hoc manner in a previous published paper. This analytical algorithm solves a tomography problem with Bayesian regularization terms in the objective function. The purpose the regularization terms is to reduce the noise in the solution.

A Bayesian objective function is set up as a functional of the image to be reconstructed. A method of calculus of variations is employed to derive a necessary condition for the optimal solution. The Euler-Lagrange equation is formed, and it leads to a filtered backprojection algorithm.

The proposed algorithm is non-iterative. Undersampled dynamic myocardial perfusion MRI data were used to test the feasibility of the proposed technique. It is shown that the non-iterative Fourier reconstruction method effectively incorporates the temporal constraint and significantly reduces the angular aliasing artifacts caused by undersampling. A significant advantage of the proposed non-iterative Fourier technique over the iterative techniques is its fast computation time.
Impact of Projection Truncation and a Small Number of Views on Image Reconstruction
Yanfei Mao, Larry Zeng

INTRODUCTION: In the conventional SPECT system, only a small portion of the detector area is used to image the heart and the rotation of the detector creates temporally inconsistent data. For human cardiac studies, the multi-pinhole system operates in mini-fication mode and a segmented parallel-hole system has better sensitivity with the same resolution, but worse data truncation. Therefore, in this paper, we focus on improving the detection sensitivity of the stationary multi-pinhole by replacing the multi-pinhole collimators with segmented parallel-hole collimators. Several possible imaging configurations using segmented parallel-hole collimation are designed and discussed at the same number of projections. The purpose of this project is to develop a revised ML-EM algorithm, investigate segmented parallel-hole collimation, and find the minimal number of view-angles.

METHOD: This work is preliminary to the design of a stationary or high-speed cardiac SPECT system. We simulated and compared three image configurations, including two segmented-parallel-hole detectors based on the conventional and large detectors, and one small multi-detector. A tailored Maximum-Likelihood Expectation-Maximization (ML-EM) algorithm, where the error-ratios outside of FOV were set to one instead of zero, before backprojection was applied in reconstructions. To study the effects of truncation and the number of angular sampling, the number of view-angles was varied from 10 to 60 and the truncation degree increased from 91% to 95%. We also test the improvements to the reconstruction results of using small detector bin size, tight support, and slight rotation. For each view-angle, the root-mean-square error (RMSE) between the reconstructed image and the phantom was calculated and used to give a measure of the accuracy of the reconstructions. Distortion was observed from the shape difference maps of the heart. A tailored Maximum-Likelihood Expectation-Maximization (ML-EM) algorithm was used in the reconstruction, wherein the true-projection to forward-projection ratios outside of FOV were set to one instead of zero before backprojection. Finally, an NCAT phantom and GATE Monte Carlo simulation tool were used to verify the conclusions.

RESULTS:

Fig 1: The reconstruction result of 20 truncated projections. Left: the image reconstructed by the conventional MLEM algorithm. 50 iterations are used. Right: the image reconstructed by the tailored MLEM algorithm. 500 iterations are used.

Fig 2: The reconstruction results of Monte Carlo simulation using the NCAT phantom. Left: conventional SPECT system with 60 views. Right: small multi-detector system with 14 views.

DISCUSSION AND CONCLUSIONS: The artifacts and distortions associated with small FOV high-sensitivity or stationary cardiac imaging can be substantially suppressed by using tailored ML-EM algorithm and small detector bin size. Two segmented conventional detector sets are sufficient to reconstruct the image without distortion, but for more accurate reconstruction, a slight rotation is required. Uniform angular sampling gives a considerable improvement in the image quality, especially in suppressing the streak artifacts in the wall of the heart. The disadvantage of the small multi-detector is that a small rotation is required to provide enough view-angles. Truncation mainly affects the reconstruction at small number of projections, in terms of reduction of the contrast. Insufficient angular sampling is the major cause of distortion. 20 views are sufficient to obtain accurate reconstruction results, even when truncation is present.

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A Multi-center trial of LGE-MRI of the left atrium
Eugene G. Kholmovski\textsuperscript{1,2}, Kavitha Damai\textsuperscript{2}, Nathan Burgon\textsuperscript{2}, Mark Haslam\textsuperscript{2}, Sathya Vijayakumar\textsuperscript{1,2}, Nassir F. Marrouche\textsuperscript{2}
\textsuperscript{1}UCAIR, Department of Radiology, University of Utah, \textsuperscript{2}CARMA Center, University of Utah

RESULTS WITHELD
Toward the development of a catheter cardiac RF coil for temperature imaging in atrial fibrillation treatment

N. A. Volland1,2,3, R. Merrill1,2, J. R. Hadley1,2,3, E. G. Kholmovski1,2,3, D. L. Parker1,2,3
1Utah Center for Advanced Imaging Research, 2Department of Radiology, 3Comprehensive Arrhythmia Research and Management Center, University of Utah, Salt Lake City, UT, United States

Purpose
The potential of MRI to allow 3D soft tissue visualization makes MRI-guided RF ablation a promising procedure for atrial fibrillation (AF) treatment [1]. With appropriate real time pulse sequences that achieve sufficient speed, resolution, and signal-to-noise ratio (SNR), the real-time control of lesion formation using MR thermometry could improve outcomes of the procedure. Previously, the acquisition of limited field of view (FOV) MR lesion or temperature images with high sensitivity within a beating heart were made possible with the use of a local RF cardiac coil placed on the heart [2]. However, to easily and minimally-invasively insert a local coil in the heart and use it clinically, the coil had to be mounted on a catheter and made foldable. For this reason, an expandable catheter-mounted local RF cardiac coil is currently being developed and evaluated.

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Group differences in resting state functional magnetic resonance imaging connectivity between individuals with autism and typically developing controls have been widely replicated for a small number of discrete brain regions, yet the whole-brain distribution of connectivity abnormalities in autism is not well characterized. It is also unclear whether functional connectivity is sufficiently robust to be used as a diagnostic or prognostic metric in individual patients with autism.

We obtained pairwise functional connectivity measurements from a lattice of 7266 regions of interest covering the entire grey matter (26.4 million connections) in a well-characterized set of 40 male adolescents and young adults with autism and 40 age-, sex- and IQ-matched typically developing subjects. A single resting state blood oxygen level-dependent scan of 8 min was used for the classification in each subject. A leave-one-out classifier successfully distinguished autism from control subjects with 83% sensitivity and 75% specificity for a total accuracy of 79% ($p = 1.1 \times 10^{-7}$). In subjects <20 years of age, the classifier performed at 89% accuracy ($p = 5.4 \times 10^{-7}$). In a replication dataset consisting of 21 individuals from six families with both affected and unaffected siblings, the classifier performed at 71% accuracy (91% accuracy for subjects <20 years of age). Classification scores in subjects with autism were significantly correlated with the Social Responsiveness Scale ($p = 0.05$), verbal IQ ($p = 0.02$) and the Autism Diagnostic Observation Schedule-Generic’s combined social and communication subscores ($p = 0.05$).

An analysis of informative connections demonstrated that region of interest pairs with strongest correlation values were most abnormal in autism. Negatively correlated region of interest pairs showed higher correlation in autism (less anticorrelation), possibly representing weaker inhibitory connections, particularly for long connections (Euclidean distance >10 cm). Brain regions showing greatest differences included regions of the default mode network, superior parietal lobule, fusiform gyrus and anterior insula.

Overall, classification accuracy was better for younger subjects, with differences between autism and control subjects diminishing after 19 years of age. Classification scores of unaffected siblings of individuals with autism were more similar to those of the control subjects than to those of the subjects with autism. These findings indicate feasibility of a functional connectivity magnetic resonance imaging diagnostic assay for autism.

We will also present our most recent findings, extending the analysis outlined above to a sample of 447 participants with autism and 517 typically developing controls.
The development of clinical tests in biological psychiatry is important from a basic science perspective, and urgent from the paradigm of translational medicine. With increased emphasis on personalized healthcare at the University of Utah, and nationally, methodological developments from functional neuroscience research are highly promising means for achieving these goals of personalized, and biologically-grounded psychiatric care. We show both the reproducibility and the uniqueness of functional brain patterns at the single subject level. We also introduce novel considerations for pattern identification in the human brain, and ways of extracting features of brain function for biological markers in psychiatric classification.
**Simultaneous Acquisition of Dual-Nuclear MR Spectroscopy (dnMRS): \(^1\text{H}\) and \(^{31}\text{P}\) MRS**

Eun-Kee Jeong\(^1\text{,}^2\text{,}^4\), Nabraj Sapkota\(^2\text{,}^3\), Josh Kaggie\(^2\text{,}^3\), Xianfeng Shi\(^2\text{,}^4\text{,}^5\)

\(^1\text{Dept. of Radiology, }^2\text{Utah Center for Advanced Imaging Research, }^3\text{Dept. of Physics, }^4\text{The Brain Institute, and }^5\text{Dept. of Psychiatry, University of Utah}\)

**INTRODUCTION:** \(^{31}\text{P}\) MR spectroscopy can provide the bioenergetics information in our body (1), while the \(^1\text{H}\) MRS is for relative concentration of a substantial number of cell specific metabolic products (2). Because of the time constraint to measure both nuclei MRS within the same acquisition session, most of MRS studies report either \(^{31}\text{P}\) and \(^1\text{H}\) MRS only. A novel acquisition method is presented to simultaneously measure \(^{31}\text{P}\) and \(^1\text{H}\) MR spectra at a clinical MRI system that is equipped with the time-sharing second RF channel. Using additional RF components and PIN-diode switches, the high frequency \(^1\text{H}\) signal is downconverted to the low \(^{31}\text{P}\) frequency, which is the carrier frequency of the measurement, and sampled at one of the \(^{31}\text{P}\) reception channels. \(^{31}\text{P}\) and \(^1\text{H}\) spins systems are manipulated within the same pulse sequence using the time-shared RF transmissions of each frequency. The residual water signal is used to identify individual \(^{31}\text{P}\) FIDs with severe phase-error due to the subject’s motion coupled with the poor shimming and to correct the phase-error on both \(^{31}\text{P}\) and \(^1\text{H}\) signals. The simultaneously acquired dual-nuclear MRS spectra may be used for direct correlation of two different MR spectra.

**METHODS:** This work requires developments of a hardware-chain that directs the \(^1\text{H}\) NMR signal toward one of the \(^{31}\text{P}\) Rx-channel and a pulse sequence that can simultaneously prepare both \(^{31}\text{P}\) and \(^1\text{H}\) transverse magnetizations within the same pulse sequence. The hardware modification, as indicated in Fig. 1, includes PIN-diode driven switches, preamplifier for 123.24 MHz \(^1\text{H}\) NMR signal, a RF mixer, a precision synthesizer, and a RF filter. Fig. 2 shows the \(^{31}\text{P}/^1\text{H}\) dn-MRS pulse sequence that can simultaneously measure both MR signals at the exact same sampling window. The gradients pulses (\(G_{xcr,y}, G_{xcr,z}\)) and (\(G_{rcr,y}, G_{rcr,z}\)) indicate the dephasing and rephrasing crusher gradients before the center of the second 90\(^\circ\) and after the center of the third 90\(^\circ\) RF pulses, respectively. \(G_{mcr,y}\) is the sum of the slice-selection and refocusing gradients for \(^{31}\text{P}\) excitation and half area of the center of the third 90\(^\circ\) RF pulses, respectively. \(G_{mcr,z}\) is the sum of the slice-selection and refocusing gradients for \(^{31}\text{P}\) excitation and half area of the center of the third 90\(^\circ\) RF pulses, respectively. \(G_{mcr,y}\) is the sum of the slice-selection and refocusing gradients for \(^{31}\text{P}\) excitation and half area of the center of the third 90\(^\circ\) RF pulses, respectively.

**RESULTS:** Raw and phase-corrected \(^1\text{H}\) and \(^{31}\text{P}\) FIDs are displayed in Fig. 3, and frequency-domain spectra are shown in Fig. 4. Several \(^1\text{H}\) FIDs were corrupted by motion-induced phase errors and corrected as shown in Fig. 1. The same motion introduced minor phase-error into \(^{31}\text{P}\) FIDs, because \(\Delta \phi_{31P}(\epsilon) = \frac{\gamma_{1H}}{\gamma_{31P}} \Delta \phi_{1H}(\epsilon) = 0.409 \Delta \phi_{1H}(\epsilon).\) \(^{31}\text{P}\) spectra in Fig. 4 are almost identical from both techniques, however, reduced SNR was observed for \(^1\text{H}\) using dnMRS because increased reflection as well as the additional noise may be introduced at the additional RF components along the \(^1\text{H}\) signal pathway in dnMRS.

**CONCLUSIONS:** Single voxel MR spectra of \(^{31}\text{P}\) and \(^1\text{H}\) were simultaneously measured using a novel acquisition method, dnMRS, at a clinical MRI system that is equipped with a timesharing RF channel. Additional hardware modification was necessary to down-convert the high-frequency proton signal to the low \(^{31}\text{P}\) frequency, which is the carrier frequency of the measurement. Localizations were independently achieved using slice-selective excitation with spatial saturations in other two dimensions for \(^{31}\text{P}\) and STEAM for \(^1\text{H}\).


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A Semi-Optimized Phased Array Coil Design for High-Resolution MRI of Cervical Spinal Cord

Nabraj Sapkota1,2, Josh Kaggie1,2, Rock Hadley2, Eun-Kee Jeong2,3,4
1Dept. of Physics, 2Utah Center for Advanced Imaging Research, 3Dept. of Radiology and 4The Brain Institute, University of Utah

INTRODUCTION: Cervical spinal cord (CSC) is a compact and one-dimensional nerve, of which cross-sectional area is about 1 cm² at the C2 level. Any injury in the CSC may lead to disability, such as in patients with multiple sclerosis and spinal cord myelopathy. Although the magnetic resonance imaging (MRI) is the most widely used non-invasive tool to evaluate the cervical spinal cord, it generally detects the lesion at the late stage. The earlier the pathological change is detected, the more option we have in the treatment. Diffusion tensor MRI (DTI) is known to be more sensitive to the earlier change in the nerve system than other conventional MRI methods, such as T1 and T2 weighted imaging. In order to detect the change in the CSC at its early stage, the high resolution imaging is needed using advanced MR imaging method and improved detections, which include the high magnetic field strength and high-sensitivity RF coil. In this work, a CSC-dedicated phased array coil is developed with its layout and the dimension optimized using computer simulation. The performance of phased array coil depends on its shape, size and number of elements. A phased array coil picks up the signal according to the Faraday’s law of electromagnetic induction. The sensitivity of a phased array coil depends on the magnetic field of the coil perpendicular to the static magnetic field. The magnitude and direction of the RF magnetic field (B1) in 3-dimensional space was calculated using the Bio-Savart’s law and the shape and size of the surface coil was optimized. An 8-channel phased array coil is constructed in the shape of human neck for CSC imaging with the eight optimized surface coils by placing them in such a way that the mutual induction between any two adjacent coils becomes zero. MRI experiments were performed to confirm the numerical simulation.

Theory: The signal voltage, which is induced on the coil from the voxel of volume V containing the magnetization per unit volume M₀ [1] V_{signal} = \omega b_{1r} VM₀ and the noise voltage picked up by received coil is given by V_{noise} = \sqrt{4kT \Delta f R}$, where b_{1r} is the transverse component of rotating magnetic field created by the unit current in the coil at the voxel of volume V, R = R_{coil} + R_{sample} \approx R_{sample} at 3 T and Δf is observational bandwidth in hertz. The Signal-to-Noise Ratio (SNR) is defined as the ratio of the signal voltage and the standard deviation of noise. For a phased array coil consisting of eight elements with the negligible mutual induction among the elements, the expression for the combined SNR can be written as

$$SNR_{combined} = SNR_{c}^2 + SNR_{s}^2 + SNR_{c}^2 \Delta + SNR_{s}^2 \Delta + SNR_{c}^2 \Delta + SNR_{s}^2 \Delta$$

METHODS: (a) Simulation: The values of the transverse component of rotating magnetic fields (b_{1r}) and sample resistances due to circular, square and rectangular coils of varying sizes have been calculated using software programmed with Matlab. (b) Experiment: For the circular, square and rectangular coils with different sizes, the SNR was measured using Gradient Echo (GRE) imaging at Siemens’ 3T. During the experiment, single surface coil was placed on the central axis where as a phased array coil constructed from eight individual coils was in cylindrical surface.

RESULTS: Matlab simulation as well as experimental result [Fig.1 and Fig.2] indicated that at the depth of 5.6 cm from the surface of planar single surface, the maximum value of SNR is achieved with a circular coil of diameter 5.0 cm. However, the square coil with 4×4 cm² also has the comparable SNR with the circular coil of diameter 5.0 cm at the depth of 5.6 cm from the coil plane. The SNR at 6 cm depth from the cylindrical surface of the 8-channel phased array coil constructed from the circular coils with diameter 8 cm is also almost comparable with that obtained using a 8-channel phased array coil constructed from the rectangular coils with 20×3 cm² [Fig.4]. The image obtained with 8-channel phased array constructed from 8 optimized circular coils has 3.90 times more SNR than the imaged obtained from Siemens’ body coil (Trio, Siemens Medical Solutions, and Erlangen, Germany) [Fig. 5].

Fig.1. Matlab simulations for the SNR due to the rectangular coils of different length and width. Rectangular coils have the length along z-axis (direction of applied field B0) and width along x-axis.

Fig.2. Experimentally measured value of SNR along the axis of the circular coils of diameter 3 cm, 5 cm, 6 cm, 8 cm and 10 cm and square coil of diameter 4 cm at the various depths.

Fig.3. 8-channel phased array coil on the surface of the cylinder of radius 6 cm.

Fig.4. Normalized SNR at the depth of 6 cm due to 8-channel phased array coil constructed on the surface of cylinder of radius 6 cm.

Fig.5. Image obtained from phased array coil (a) and from the Siemens’ body coil (b).

CONCLUSIONS: At a specific depth from a single-planar surface coil, the maximum SNR is achieved with a particular size and shape of the coil. The SNR using the optimal circular and square coils are almost the same for a given depth. However, among the family of rectangular coils, square coil with optimal size has better SNR than any other rectangular coils for the given depth. ACKNOWLEDGEMENT: This work was partially supported by VA Merit Review Grant and Ben B. and Iris M. Margolis Foundation.

Measurement of Brain Metabolites using Lactate Enhanced Detection CSI (LED-CSI) Pulse Sequence

X.F. Shi1,2, Andrew Paul Prescot2,3, Y.H. Sung1,2, Douglas Kondo1,2, S.E. Kim3, E.K. Jeong2,3 and Perry F. Renshaw1,2
1Dept. of Psychiatry, 2The Brain Institute, and 3UCAIR/Dept. of Radiology, University of Utah, Salt Lake City, Utah

INTRODUCTION: Numerous reports indicated that the elevated lactate metabolite concentration in brain was observed from patients with psychiatric disorders such as bipolar, schizophrenia, and depressive disorders. The pathophysiologic mechanism that underlies this metabolic change is uncertain. One hypothesis is that the oxidative metabolism using glucose is dysfunctional in mitochondria. Therefore, glycolytic conversion of pyruvate to lactate acid is activated to compensate for the insufficient energy supply in order to maintain normal brain activity. At TE=135 ms, the lactate doublet resonance is negative in phase which is easy to recognize and fit. However, the challenge associated with lactate detection at TE=135 ms is signal nulling due to the four compartment artifact [1]. This makes the lactate concentration evaluation difficult. Although single voxel spectroscopy (SVS) with lactate detection improvement has been investigated by others [2, 3], there is no detailed report regarding optimization of lactate signals in CSI experiments. This report describes lactate signal behavior using lactate enhanced detection CSI pulse sequence (LED-CSI) which minimizes the four compartment artifact and enhance the lactate and glutamate/glutamine signal detection.

METHOD: Fig. 1a illustrates LED-CSI sequence diagram. A non-selective adiabatic B1 independent rotation-4 (BIR4) pulse is added to conventional CSI pulse sequence. The BIR4 is placed in the middle of time interval between the first and the second selective 180° RF pulses. This BIR4 re-phases the phase dispersion resulting from J-coupling between the lactate methyl group protons and the methine group proton. Fig. 1b demonstrates the molecular structure of the lactate. The red circle includes methyl group protons while the green cycle contains the methine group proton. The chemical shift displacement between the methyl group protons (red matrix) and the methine group proton (green matrix) at 3T is about 342 Hz which is 84 mm with respect to the 200 mm field of view shown in Fig. 1c.

RESULT & DISCUSSION: Fig. 1e would show almost no lactate signal (green) if the conventional CSI sequence is used at TE=135 ms. With LED-CSI, the lactate signal (red) is greatly recovered as shown in Fig. 1f. In addition, glutamate signal in LED-CSI is also improved compared to Fig. 1e (red and green arrow). Benefits of choosing TE 135 ms include reduced macromolecule and lipid signals. Even with any residual macromolecule/lipid signal, the negative lactate doublet is also easy to be identified and distinguished from macromolecule signals, which are positively phased. Introduction of the adiabatic BIR4 RF pulse minimizes the signal loss due to the imperfect 180° RF pulse. Compared to the conventional LASER pulse sequence, LED-CSI results in less specific absorption rate (SAR) problems and is relatively easy to be implemented. With respect to the SIS, LED-CSI shows much stronger Lactate/Glutamate/Glutamine SNR enhancement and has the potential to play a critical role in monitoring lactate and glutamate/glutamine variation.


Fig. 1: (a) LED-CSI sequence diagram, (b) Lactate molecule: methyl group is circled in red and the methine group proton is shown in green. (c) Chemical shift displacement of methyl group protons (red) and methine group proton (green). PE: phase encoding; RO: readout direction. (d) Region of Interest. Blue box represents the typical chemical shift imaging voxel. (e) and (f) are spectra acquired using conventional CSI and LED-CSI, respectively.
Background: Converging evidence from neuroimaging and neuropsychological studies indicates that heavy marijuana use is associated with cingulate dysfunction (1). Recent studies performed in younger subjects suggest that prefrontal cortical functional and structural alterations are detectable in adolescent chronic marijuana users compared to non-using control subjects (2, 3). Δ⁹-tetrahydrocannabinol (THC), the primary psychoactive compound within marijuana smoke, activates the cannabinoid type-I (CB1) receptor, a Gᵢ/Gₒ-protein-coupled receptor enriched and distributed throughout the mammalian brain. Activation of the CB1 receptor is known to inhibit presynaptic Ca²⁺ influx, which in turn decreases the probability of neurotransmitter release. Retrograde inhibition of neurotransmission has been reported for both γ-amino butyric acid (GABA) and glutamate (Glu) neurons throughout the whole brain (4) and individual brain structures (5). GABA, Glu, and their respective receptor systems are known to play a critical role in cortical remodeling throughout adolescence (6), and a key question is whether chronic exposure to exogenous cannabinoids during adolescence results in detectable alterations of these important neurotransmitter systems, and GABA and Glu metabolism. We recently employed proton (¹H) magnetic resonance spectroscopy (MRS) methods to non-invasively measure anterior cingulate cortex (ACC) metabolism in adolescent chronic marijuana smokers, identifying significantly lower in ACC Glu levels compared to non-using controls (7). For the present study, metabolite-editing ¹H MRS methods were used to measure ACC GABA using a similar adolescent cross-sectional study design. We hypothesized that lower ACC Glu levels are paralleled by comparable reductions in ACC GABA levels.

Methods: Adolescent marijuana (MJ) users (N = 13; average age 18 ±1 years) and similarly aged healthy control (HC) subjects (N = 16; average age 16 ±2 years) were enrolled and scanned using a Siemens 3T Trio MRI system. Clinical variables taken from all MJ subjects included age of first use, age of regular use and total marijuana use. Conventional (PRESS) and GABA-editing (MEGAPRESS) ¹H MRS methods were used to acquire metabolite and unsuppressed water MRS data from a 22.5 mL voxel positioned bilaterally within predominantly gray matter of the ACC. MEGAPRESS ¹H MRS spectra were fitted using automated MATLAB routines developed in-house, and GABA levels were normalized to a scaled unsuppressed water PRESS signal integral corrected for CSF fraction. Group mean metabolite levels were statistically evaluated using two-tailed t-tests.

Results and Discussion: GABA levels were significantly lower in the MJ cohort (MJ 0.63 ±0.12; HC 0.81 ±0.25) and, in agreement with our previous study, the MJ cohort showed significantly lower ACC Glu (MJ 4.84 ±0.52; HC 5.61 ±0.88) levels. Statistical significance remained for both GABA and Glu after co-varying for subject age. In addition, correlation analysis showed a trend towards a significant negative relationship between GABA levels and total MJ use (Pearson product moment: r = -0.54, p = 0.06). These results further expand on previous functional imaging data reporting altered cingulate function in adolescent and adult humans with marijuana-abuse, demonstrating that prefrontal Glu abnormalities are paralleled by lower prefrontal GABA levels. These findings may reflect THC-induced disruption of the endocannabinoid system, which plays an important role in synaptic plasticity by regulating of GABA and Glu release at presynaptic neurons. Future clinical and preclinical investigations are warranted to further illuminate the underlying neurobiological and neurochemical changes associated with adolescent cannabinoid exposure. This presentation will briefly introduce the rationale behind our ongoing investigations using optimized 2D ¹H MRS procedures (8) in human subjects, as well as proposed multinuclear MRS studies as applied to established rodent models.

PNS Safety of the Composite Gradient System

KC Goodrich, SE Kim, J Kaggie, JR Hadley, R Merrill, DL Parker

Introduction: This work presents the results from 3-axis peripheral nerve stimulation (PNS) comparison studies using 1) body gradients only, 2) insert head/neck gradients only, and 3) simultaneous operation of body and insert gradients (composite mode). Methods: With IRB approval and informed consent, 10 volunteers underwent nerve stimulation testing using our composite gradient system. Tests were performed in a Siemens 3T TIM Trio scanner (Siemens Medical, Erlangen Germany) equipped with TQ body gradients and a gradient insert designed for neck and head imaging. The system has three extra gradient amplifiers and master/slave configured computers capable of controlling extra gradient channels. The master computer controls the standard body gradients and triggers the slave computer to run the insert synchronously with the standard gradients, creating an imaging gradient equal to the sum of the two component gradient systems. Volunteers were positioned with their head centered radially and completely inside the insert gradient with shoulders touching the edge of the insert. The linear region of the insert was aligned with the isocenter of the whole-body gradients for all tests (as would be standard for head imaging with this system). The three gradient configurations were measured in random order. The pulse sequence consisted of 64 1ms trapezoid pulses with slew time of 400 μsec (from max. positive to max. negative amplitude), which was repeated 10 times with a TR of 1s. After each scan, assessment of nerve stimulation location and sensation (twitch, poke) were recorded. Double Mode (DM): Five volunteers were tested with the insert operating equal to the body gradient strength. For this study, a single volunteer repeated the Y stimulation measurement 7 times to estimate error. Triple Mode (TM): Five volunteers were tested with the insert operating at double the body gradient strength creating an effective gradient triple to that of the standard body gradient field. Individual components of the TM composite field were separated into body and insert contributions (1/3 and 2/3 respectively). The TM composite X gradient field (xC3) equals the x-contribution from the body gradient (xCb) and the x-contribution from the insert gradient (xCi). Body and insert only x-gradients are referred to as xB and xI2, respectively. Similar relations apply for the Y gradient.

Results: Volunteers typically reported torso PNS induced by body only operation and head PNS by insert only operation. Double Mode: No volunteer stimulated during insert only operation. All composite mode stimulation thresholds were above those measured for the body only operation. For a single volunteer, the slew rate threshold reproducibility error estimate was 99.4±5.6 T/m/s. Triple Mode: Some of the volunteers were stimulated when the insert was set to double body gradient strength. Stimulation thresholds for the composite mode were consistently higher than either the insert only or body only configurations. Table 1 lists the number of volunteers stimulated with each configuration.

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Discussion and Conclusions: The composite mode stimulated when either the body gradient or insert gradient components reached the same stimulation thresholds that they achieved in their individual modes. Figure 1 compares composite field components with body only and insert only mode thresholds. In Fig 1a), the stimulation thresholds for the insert only gradient (xI2) were essentially the same magnitude as the insert component of the composite gradient (xCi), indicating an insert gradient dominant stimulation. Stimulation locations during X Gradient experiments both occurred in the head, further indicating insert gradient dominant stimulation. In Fig Ib), the stimulation thresholds for the body only gradient (yB) were essentially the same magnitude as the body component of the composite gradient (yCb), indicating a body gradient dominant stimulation. The Y Gradient experiments both resulted in torso stimulation, further indicating body coil dominant stimulation. These results suggest that body and insert gradient thresholds are independent of each other, allowing for increased combined gradient field strength and slew rates in composite mode until either constituent threshold is reached. These results show a definite safety advantage for composite gradient mode operation allowing larger gradients and slew rates.

![Figure 1](image-url) Triple Mode a) X and b) Y Gradient PNS Thresholds. a) Insert gradient dominant threshold. The body contribution (xCb) to composite operation did not reach the PNS threshold for the body only mode (xB). While the insert contribution (xCi) is close to the insert only mode (xI2) for all volunteers. b) Body gradient dominant threshold. Insert only thresholds (yI2) are much higher than the body gradient portion (yCi) of the composite and do not seem to be the limiting element for composite thresholds. Body gradient portion thresholds (yCb) more nearly match the body only thresholds (yB). yCb+yCi=yC3, yCb*2=yI2.

References:

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