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14. ABSTRACT There is no clinically applicable mechanism to noninvasively image the insulin-producing beta-cells of the pancreas. Individuals only become aware of having developed type I or type II diabetes (T1D or T2D, respectively) following the appearance of overt hyperglycemia. Our objective was to utilize advanced high-resolution magnetic resonance spectroscopy (MRS, a form of MRI) to noninvasively measure the small molecule constituents of the pancreas (i.e., define the pancreatic "MRS-ome") in a living large animal model (swine). As a proof-of-principle, we planned to determine whether 2D-MRS can detect the loss of the insulin-producing beta-cells which underlies T1D in a swine. Just after obtaining institutional approval to conduct the animal studies the pandemic hit. Because of the large number of veterinarians and MRI staff needed to anesthetize, monitor vitals, and MRI image large animals, our studies could not be conducted due to limitations on the number of people allowed per square foot. We shifted to improving the imaging parameters to achieve much shorter data acquisition times which will be very helpful for future MRS imaging of live animals.

15. SUBJECT TERMS
None listed.

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1. Introduction

Diseases of the pancreas are common and include pancreatitis, pancreatic cancer, and type 1 and type 2 diabetes (T1D and T2D). It would be very beneficial to discover and implement new technologies to monitor pancreatic cells in health and disease states. Magnetic resonance imaging (MRI) uses magnetic fields, radio waves, and computer analysis to noninvasively and safely obtain detailed anatomical information. Magnetic resonance spectroscopy (MRS) can be performed together with MRI using conventional hospital MRI scanners in order to provide detailed biochemical information on the constituents within a region of interest. MRS has been clinically applied to noninvasively characterize changes in small molecules levels in the brain, breast, and prostate that are associated with disease. MRS, however, has not been well-developed to monitor small molecules in the pancreas that could provide new biomarkers of pancreatic diseases and read-outs of the efficacy of therapeutic interventions. We will for the first time, utilize advanced high-resolution 2 dimensional (2D) MRS to noninvasively measure the small molecule constituents of the pancreas (i.e., define the pancreatic “MRS-ome”) in a living large animal model. Next, as a proof-of-principle, we will determine whether 2D-MRS can detect the loss of the insulin-producing beta-cells which underlies T1D in this large animal model. Currently, there is no clinically applicable mechanism to noninvasively image the beta-cells and individuals only become aware of having developed T1D or T2D following the appearance of overt hyperglycemia. We anticipate that 2D-MRS will provide new noninvasive biomarkers of beta-cell mass. Such biomarkers are currently highly sought after in order to aid in the evaluation of therapeutics designed to inhibit or reverse T1D and T2D. Because MRS is safe, it can be repeatedly used to monitor disease progression and the efficacy of therapeutics. Additionally, the technology can be applied to aid in the diagnosis and treatment of other pancreatic disorders such as pancreatitis and pancreatic cancers. We anticipate that by providing clinicians with entirely new noninvasive read-out of the abundance of an array of pancreatic small molecules it will lay a foundation for better understanding the molecular basis of many pancreatic diseases. It will also provide new noninvasive biomarkers that could revolutionize medical treatments of pancreatic disorders by allowing early diagnosis and new detailed read-outs of pancreatic constituents that may allow better personalized treatments.

2. Keywords

Pancreas
Diabetes
noninvasive imaging
Magnetic resonance imaging
Magnetic resonance spectroscopy

3. Accomplishments.

Due to the pandemic, we had to put on hold our plans to conduct live animal MRS studies since the large number of people needed in the room would exceed the limits of the allowable indoor density at UCLA. We thought there would be a lessening of the these space requirements in fall 2020, but the spike in COVID-19 cases following Thanksgiving, along with our need to image the same animal longitudinally, before and after type 1 diabetes onset, prevented us from moving forward. Rather we, switched to improving the parameters for large animal MRS imaging using "phantoms" (nonliving control objects). We developed an accelerated version of localized correlated spectroscopy (L-COSY) sequence on the Siemens 3T MRI scanner. The earlier version of 2D L-COSY requires <30 minutes of data acquisition. We developed 2X, 2.5X and 3X versions resulting in total acquisition durations of 15, 12 and 10 minutes and we acquired phantom scans.
The specific data are shown below.

The 2D localized correlated spectroscopy (L-COSY) sequence uses three slice-selective radio-frequency pulses (90°-180°-90°) along three orthogonal directions as reported by Thomas et al.[1] A voxel size of 2×2×2 cm^3 can be localized for *in vivo* applications at 3T. The indirect (t_1) dimension has been non-uniformly undersampled (NUS) at accelerations of 2×, 3× and 4×, and the 2D L-COSY spectra has been acquired using the following parameters: TE/TR = 22ms/2500ms, 2048 t_2 points, 96 Δt_1 increments with 8-16 averages per increment, and a 9-20 minute total scan time. The t_1 increment duration was 0.8 ms with corresponding bandwidths of F_2/F_1 = 2000Hz/1250Hz. A water-unsuppressed scan using 1 average has also been acquired for eddy current and phase correction, and coil combination. Scans have been acquired using a brain phantom and a 16-channel receive head coil on the Siemens 3T whole-body MRI scanner.

The accelerated L-COSY raw data was extracted from 16 channels using a home-built MATLAB library. Zeroes will be added to all missing data points. The coil sensitivities (S) were determined from the non-water-suppressed reference scan by taking the first time point and dividing each channel by their sum of squares. The first time point will be chosen because each resonance is in phase at the echo time. A region of interest (ROI) was also estimated from the reference sum-of-squares image where the intensities were greater than twice the mean. Qualitative comparison is performed between a mixed-norm group sparse[2] (GS) reconstruction and a Joint Hankel Low Rank[3] (JHLR) reconstruction using different undersampling factors with single channel and multichannel data (Figure 1).

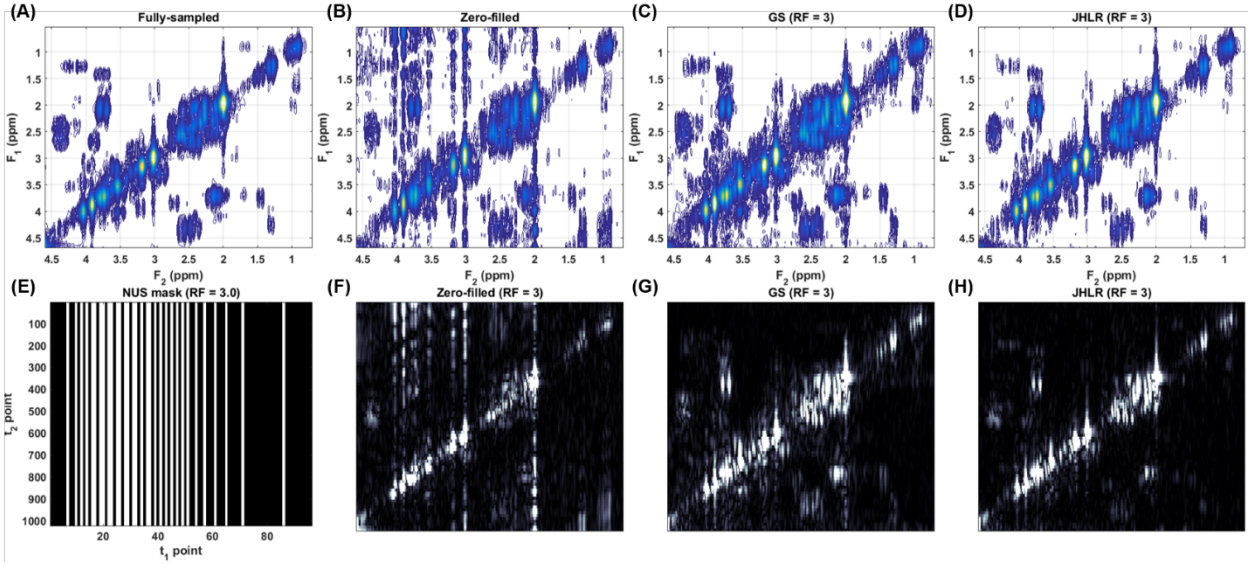

Figure 1: **(A)** Fully-sampled L-COSY in a brain phantom **(B)** L-COSY spectrum from a zero-filled reconstruction **(C)** L-COSY reconstruction using Group Sparsity (GS) **(D)** L-COSY using Joint Hankel Low Rank-based (JHLR) reconstruction **(E)** Non-uniform undersampling (NUS) mask for an acceleration factor of 3×. (F) Difference between the zero-filled and fully-sampled reconstructions **(G)** Absolute difference between the fully-sampled and GS reconstructions **(H)** Absolute difference between the fully-sampled and JHLR reconstructions. Note the reduced reconstruction error of JHLR compared to GS from the difference maps in (G) and (H).

[1] Thomas, M. Albert, et al. "Localized two-dimensional shift correlated MR spectroscopy of human brain." *Magnetic Resonance in Medicine* 46.1 (2001): 58-67

[2] Burns, Brian L., Neil E. Wilson, and M. Albert Thomas. "Group sparse reconstruction of multi-dimensional spectroscopic imaging in human brain in vivo." *Algorithms* 7.3 (2014): 276-294

[3] Saucedo A., Sarma M.K, Thomas M.A. Accelerated Localized Correlated Spectroscopy with Compressed Sensing Reconstruction Using Joint Hankel Low Rank Regularization and Group Sparsity. In Proceedings of the 26th Annual Meeting of ISMRM, Paris, France, 2018. Abstract #3530.

4. Impact

We were not able to conduct the main goal of this proposal due to the pandemic. We shifted to improving the imaging parameters to achieve much shorter data acquisition times which will be very helpful for future MRS imaging of live animals.

5. Changes/Problems

We were not able to conduct the main goal of this proposal due to the pandemic. We shifted to improving the imaging parameters to achieve much shorter data acquisition times which will be very helpful for future MRS imaging of live animals.
At the time of writing June 2021, UCLA is now re-opening. In the future, we hope to use our uncommitted funds to conduct a pilot study that will begin to test the hypothesis that MRS can monitor ß-cell mass in swine.

6. Products Nothing to report

7. Participants & Other Collaborating Organizations

Name Daniel Kaufman
Role PI
Person month worked 1 calendar month
Contribution: Wrote imaging protocols and obtained institutional approval to work with swine. Communicated with MRI facility regarding imaging protocols.

Name Albert Thomas
Role Co-investigator
Person month worked 1 calendar month
Contributions: Worked with Mr. Saucedo to develop an accelerated version of localized correlated spectroscopy (L-COSY) sequence

Name Andres Saucedo
Role GSR
Person month worked 2 calendar month
Contribution: Mr. Sauedo developed an accelerated version of localized correlated spectroscopy (L-COSY) sequence and conducted and analyzed MRS studies with phantoms (see in results)

Name Jhelum Paul
Role SRA
Person month worked 2 calendar month
Contribution: Ms. Paul helped developed an accelerated version of localized correlated spectroscopy (L-COSY) sequence and conducted MRS studies with phantoms

Name Blake Middleton
Role SRA III
Person month worked 6 calendar months
Contribution: Helped write imaging protocols and obtained institutional approval to work with swine. Took the lead in preparing lab for ramp-down and ramp down protocols due to COVID-19. Conducted and analyzed MRS studies with phantoms containing dose ranges of GABA.

Name Min Song
Role SRA III
Person month worked 3 calendar months
Contribution: As lab manger she ordered supplies, prepared lab for ramp-down and maintenance during COVID-19 ramp down.

Changes in PI funding:

New awards:

R21 DE029020 (Kaufman PI) 2019-07-01 - 2021-06-30
National Institutes of Health
Oral GABA treatment as a novel and safe therapy to ameliorate Sjogren's Syndrome
Dr. Kaufman 1.2 calendar month effort

2-SRA-2021-1028-S-B (Xia Yang PI) 51/1/21-4/30/23
Juvenile Diabetes Research Foundation
Network-based Systems Biology for T1D Drug Repositioning
Dr. Kaufman 0.9 calendar month effort

Awards that ended:

RG-1607-24947 (Kaufman PI) 4/1/2017-3/30/2020
National Multiple Sclerosis Society (Kaufman PI)
Preclinical studies aimed at repurposing a clinically safe drug to help treat MS

Department of Defense CDMRP PR191176 (Kaufman PI) 3/1/20-2/29/21
New noninvasive biomarkers for the diagnosis and treatment of pancreatic disorders
We will try to develop magnetic resonance spectroscopy to ascertain the levels of small molecules in the healthy and diabetic pancreas of living animals.

8. Special Reporting Requirements - not applicable

9. Appendices - None