Evaluation of Heterogeneous Metabolic Profile in an Orthotopic Human Glioblastoma Xenograft Model Using 3D Compressed Sensing Hyperpolarized 13C MRSI

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Introduction: Dynamic Nuclear Polarization (DNP) and the development of a dissolution process have enabled the real time monitoring of ^{13}C metabolism *in vivo* at very high SNR [1]. Due to T1 decay of the hyperpolarized signal, fast imaging techniques, such as compressed sensing, have been incorporated in the acquisition of hyperpolarized ^{13}C data [2]. In this project, we modified a previous compressed sensing scheme to achieve a x3.72 acceleration and a factor of 4 increase in resolution. The new design was validated through phantom experiments and by comparing with fully sampled ^{13}C 3D MRSI data. The new compressed sensing method was applied to an orthotopic human xenograft tumor model in rat brain in order to demonstrate the utility of using this technique to evaluate heterogeneous ^{13}C metabolic profiles within brain tumor tissue.

Design of Compressed Sensing Scheme: The new compressed sensing scheme, tailored for the application in this rat brain study, was designed following the framework provided in a previous report [2]. A x3.72 acceleration was achieved by acquiring a 20x16 matrix with 24 fully sampled central encodes, 38 encodes with x4 undersampling, and 24 encodes with x6 undersampling.

Methods: Athymic rats were intracranially implanted with human glioblastoma cells (U-87 MG) in order to create an orthotopic brain cancer model [3]. All experiments were performed using a GE EXCITE 3T scanner with a custom-designed $^{1}H/^{13}C$ rat coil. In order to validate the new design, a spherical phantom containing enriched ^{13}C acetate was scanned using the newly designed compressed sensing ^{13}C 3D MRSI sequence. For rats with brain tumors, we pre-polarized 35µL (100 mM) of [1-^{13}C]-pyruvate (with 1.5 mM gadolinium) using a Hypersense® DNP polarizer (Oxford Instruments, Abingdon, UK). Both compressed sensing and fully sampled ^{13}C 3D MRSI data were acquired using a double spin echo sequence (TE/TR=140/215 ms) with centric k-space encoding, a variable flip angle scheme and echo-planar readout [2] at 20 sec after the injection of approximately 2.5 ml hyperpolarized [1-^{13}C]-pyruvate through the tail vein. For the compressed sensing acquisition with x3.72 acceleration, 86 phase encodes were collected from a 20x16 matrix in 18 sec, resulting in 2x2x5.4 mm resolution. For the fully sampled acquisition, 80 phase encodes were collected from a 10x8 matrix in 17 sec, resulting in 4x4x5.4 mm resolution. The compressed sensing data were reconstructed using the same methods and parameters described previously [2]. T1-weighted spin-echo images (TE/TR=10/700 ms, 1.2 mm slice thickness) were acquired in axial plane after the injection of 0.2 mmol/kg Gadolinium (Gd)-DTPA to define the extent of tumor. The brains of two rats were resected and stained with H&E for histological analysis.

Results: Figure 1 shows a T2-weighed image and compressed sensing ^{13}C MRSI data from the acetate phantom. The location of ^{13}C acetate signal was consistent with the shape and location of the phantom from the anatomical scan. Figure 2 shows a comparison between the compressed sensing and fully sampled ^{13}C spectra acquired in consecutive scans from a rat with brain tumor. The x3.72 undersampled compressed sensing reconstructed data were in excellent agreement with the fully sampled data. Interestingly, the compressed sensing data revealed heterogeneous metabolic profiles within a contrast-enhancing (CE) lesion (highlighted voxel in Figure 2). Two highlighted voxels on the right had highly elevated lactate peaks compared to the voxels on the left. Figure 3 shows another example of a rat with brain tumor. T1 post-Gd images displayed a dark region surrounded by the CE lesion in the anterior part of the brain. The corresponding voxels (blue) from the compressed sensing ^{13}C spectra showed decreased pyruvate signal and negligible lactate signal. In contrast, voxels in the CE lesion (red) had elevated pyruvate and lactate signal. The corresponding H&E stained slice showed several areas with substantial amount of necrosis and fibrosis in the region corresponding to the blue voxels, while the sections of tumor corresponding to the red voxels showed minimal or no necrosis and fibrosis. Figure 4 shows a rat with a uniform CE lesion. The compressed sensing spectra exhibited highly elevated lactate and pyruvate peaks in the CE lesion. The corresponding H&E slice showed no necrotic or fibrotic tumor cells.

Conclusions: We have demonstrated the feasibility of using compressed sensing hyperpolarized ^{13}C 3D MRSI to evaluate heterogeneous metabolic profiles in an orthotopic human xenograft model of rat brain tumor. The 3.72-fold acceleration factor in our new compressed sensing design developed in this project allowed the reliable acquisition of hyperpolarized ^{13}C 3D MRSI data with a factor of 4 increase in resolution in approximately the same scan time compared to fully sampled ^{13}C 3D MRSI data. Our results suggest that this technique may be used to differentiate brain tissue with different tumor histology.

References: [1] Ardenkjaer-Larsen et al., Proc Natl Acad Sci USA, 2003;100:10158-63 [2] Hu et al., Magn Reson Med, 2010;63:312-21 [3] Park et al., Neuro Oncol, 2010;12:133-44

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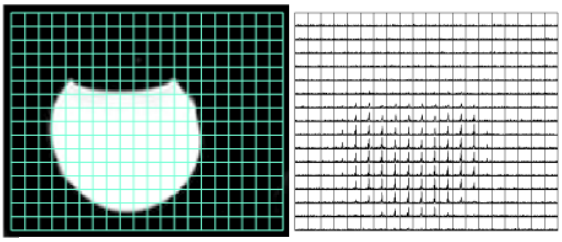

Figure 1: Phantom validation data acquired using the new compressed sensing design. The location of ^{13}C acetate signal (right) is consistent with a T2 weighted image of the phantom (left).

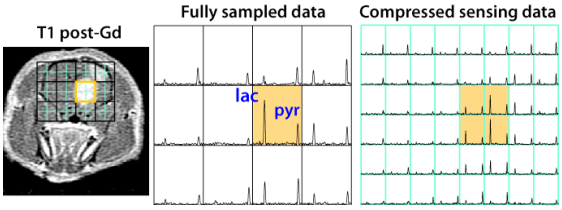

Figure 2: Comparison of compressed sensing and fully sampled ^{13}C 3D MRSI data acquired in successive scans. The undersampled compressed sensing data set matched the fully sampled data set extremely well.

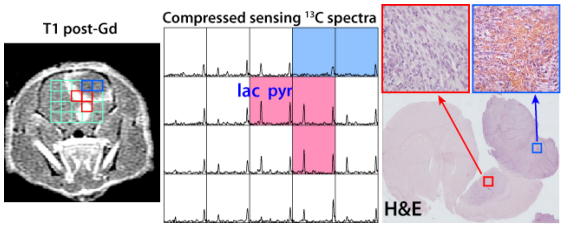

Figure 3: An example of a rat with a necrotic region inside the CE lesion. Necrotic tissue (blue) and non-necrotic tumor tissue (red) exhibited distinct ^{13}C metabolic profiles from compressed sensing data. H&E slices confirmed substantial necrosis and fibrosis in the blue region while the red region had no necrosis.

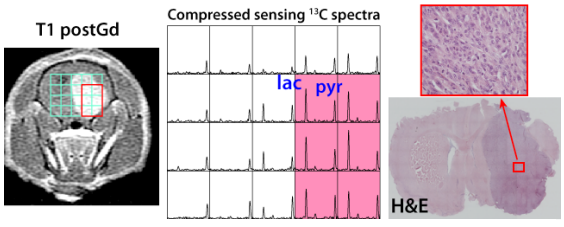

Figure 4: An example of a rat with a uniform CE lesion. Compressed sensing ^{13}C spectra displayed highly elevated lactate and pyruvate signal in the corresponding voxels (red). H&E staining showed no sign of necrosis in the tumor.