

Dynamic Deuterium MRS Imaging of Brain Tumor with Enhanced Sensitivity and Spatiotemporal Resolution

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Synopsis

Noninvasive MR-based metabolic imaging of brain tumor may offer new tools for clinic diagnosis and monitoring of tumor growth or assessment of treatment efficacy. One potential candidate is the dynamic deuterium MRS (DMRS) imaging technique recently developed. To reach its full potential, we integrated advanced data processing with D-MRSI to enhance its sensitivity or spatiotemporal resolution. We demonstrated in this pilot study that quantitative “Warburg Effect” map and kinetic time courses of deuterated metabolites can be achieved with good spatiotemporal scales in rat brain tumor using Deep-SPICE based deuterium MRSI, which could potentially be applied to brain tumor patients.

INTRODUCTION

Recently, we developed a novel metabolic imaging technique based on the *in vivo* deuterium (²H) MRS (DMRS) approach to quantitatively and simultaneously measure the cerebral metabolic rates of glucose consumption, TCA cycle and lactate (Lac) production.¹ It has been shown that this neuroimaging technique is capable of assessing the “Warburg effect” in preclinical animal model and human patients with brain tumor;²⁻⁴ thus it could have a high potential for translational applications. However, similar to other X-nuclei MRS imaging techniques, ²H MRS imaging (DMRSI) also suffers from low detection sensitivity and low metabolite concentration that seriously limits its utility. In this work, we demonstrate that by applying the SPICE-based reconstruction method,⁵ the SNR of the DMRS signals can be significantly improved and 3D dynamic high-resolution deuterium images were obtained at 16.4T from rat brain tumor.

METHODS

***In vivo* DMRSI measurement:** Male and female Fischer rats with implanted gliosarcoma (GS-9L cells, Sigma-Aldrich) were scanned under 2% isoflurane anesthesia. Their femoral arteries and veins were catheterized for blood sampling, physiological monitoring and deuterated glucose infusion. All MR experiments were conducted on a 16.4 T/26 cm scanner (Varian/VNMRJ) using a passively decoupled ¹H/²H surface coil. High-resolution dynamic 3D ²H-CSI with ~10 μ L nominal voxel size (17x17x5 matrix and 28x28x24mm³ FOV) and 105s per CSI volume were acquired from the rat brains before, during and after the 2.5min i.v. infusion of D-Glucose-6,6-d2 (1.3 g/kg-BW dissolved in 2.5 mL saline, Sigma-Aldrich). All resonance signals of deuterated water, glucose (Glc), Glx (glutamate/glutamine) and Lac were analyzed and high-resolution images of Lac and Glx, and the Lac/Glx ratio images were generated.

Deep-SPICE data processing method: Reconstruction of the desired spectral and temporal functions from the acquired ²H-MRSI data was accomplished by leveraging both physics model-based and data-driven priors. For the model-based priors, we used a subspace-based signal representation incorporating pre-learned spectral basis functions from high-SNR training datasets. For data-driven priors, we estimated the prior distributions of spectral and temporal functions using deep learning (DL) and incorporated them into the solution. Image reconstruction was formulated as solving the following optimization problem (voxel-by-voxel, ignoring the spatial coordinates):

Equation 1 (1)

where d is the measured data, F the imaging operator, $\phi(f)$ the pre-learned spectral basis, $\rho_g(f, T)$ the ML-based prior, $KL(\cdot||\cdot)$ the KL-divergence and δ some preset threshold.

RESULTS

Figure 1 shows typical ²H MRS imaging obtained from a representative rat with brain tumor. The original natural abundance deuterium water signals distribution averaged from five CSI volumes pre-D66 infusion were displayed. The corresponding Lac and Glx images and Lac/Glx ratio maps generated using Deep-SPICE processing method were overlaid on the corresponding anatomic image where location of the brain tumor is evident. **Figure 2** displays the original deuterium spectra obtained from a single 10 μ L voxel located either in tumor or non-tumor brain region as indicated in **Fig. 1** with an acquisition time of $T_{acq} < 2$ min. As a comparison, the corresponding spectra using Deep-SPICE processing method were shown in the same plot. Utilizing this newly developed post-data process method offering a large SNR improvement, we can evaluate crucial metabolic information and dynamics of the brain tumor from the time courses of key deuterium-labeled metabolites involved in the cerebral glucose metabolism. As shown in **Figure 3**, we found that the Lac/Glx ratio in the tumor region is ~10 times higher than the corresponding non-tumor region in this particular rat.

DISCUSSION and CONCLUSION

The *in vivo* ²H-MRS imaging technique with improved sensitivity and spectral resolution at high/ultrahigh field has shown promises for studying abnormal glucose metabolism and TCA cycle activities in brain tumor.¹⁻⁴ However, to further push the spatiotemporal resolution of DMRS-based metabolic imaging, it requires advanced data processing. The Deep-SPICE method was developed for improving the sensitivity and/or spatiotemporal resolution by effectively incorporating physics-based and data-based prior information. This approach was successfully applied in present study to evaluate the metabolic alterations in a rat model of gliosarcoma. We observed elevated lactate production and suppressed TCA cycle activity, a clear sign of “Warburg Effect” in the rat brain at the site of gliosarcoma,⁶ while normal glucose metabolism with high ²H-labeled Glx and low ²H-Lac were observed in corresponding normal appearing tissue. The improved DMRS sensitivity offered by the Deep-SPICE method allows us not only to generate high-resolution images of different metabolites or their ratios for assessing the brain tumor, but also to monitor their dynamic changes over the time, thus making it possible to calculate voxel-based metabolic rates from the dynamic data with largely enhanced temporal resolution and/or characteristics. Here we found that the differences between the tumor and non-tumor Lac/Glx ratios can reach ~10 times, which could be used as a sensitive measure of the tumor severity reflecting the degree of the “Warburg Effect” in brain tumor. This DMRSI-Deep-SPICE approach with further validation on metabolic quantification could provide a highly valuable and robust tool for DMRS-based metabolic imaging in brain tumor research and potentially for clinical translation.

Acknowledgements

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References

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Figures

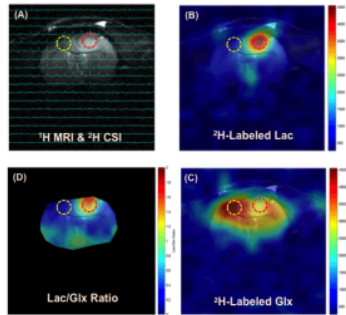


Figure 1. Data obtained from a representative rat with implanted 9L brain tumor: (A) natural abundance D_2O image from original 3D-CSI data with $T_{\text{acq}}=8.75\text{min}$ overlay on the corresponding ^1H MRI; Similar images of ^2H -labeled Lac (B) and Glx (C) generated from CSI data acquired ~30-60min after the D66 infusion; and (D) the corresponding Lac/Glx ratio map. The data shown in (B)-(D) were processed using Deep-SPICE method; and the yellow and red circles represent the CSI voxels located in the non-Tumor and Tumor brain regions, respectively.

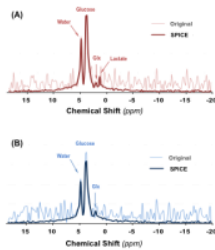


Figure 2. Representative ^2H MR spectra obtained with $10\mu\text{l}$ CSI voxel size and 105s per volume from a single voxel located in Tumor (A) and non-Tumor (B) regions, respectively. Both original and SPICE processed spectra are shown herein.

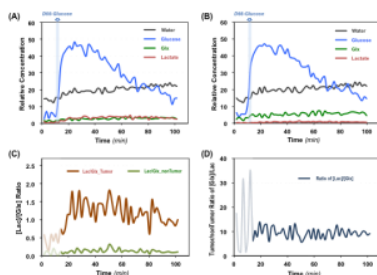


Figure 3. The time courses of the metabolites concentration detected in the Tumor (A) and non-Tumor (B) voxels are displayed for deuterium labeled Water, Glucose, Glx and Lactate, respectively. The dynamic changes of the [Lac]/[Glx] ratios (define as Warburg Effect index) in Tumor and non-tumor voxels are shown in (C); and (D) presents the Tumor/non-Tumor ratio of the Warburg Effect index indicating ~10 times differences in this rat brain tumor as compared to the normal appearing brain tissue.

$$\begin{aligned} & \min_{\{a_\ell(T)\}} \|d - F(\sum_{\ell=1}^L a_\ell(T) \varphi_\ell(f))\|_2^2 \\ & \text{subj. to } KL(\rho_g(f, T) \| \sum_{\ell=1}^L a_\ell(T) \varphi_\ell(f)) \leq \delta, \end{aligned}$$

Equation 1 In this equation, d represents the measured data, F the imaging operator, $\varphi_\ell(f)$ the pre-learned spectral basis, $\rho_g(f, T)$ the ML-based prior, $KL(\cdot \| \cdot)$ the KL-divergence and δ some preset threshold.