

Reproducibility of 2-hydroxyglutarate spectroscopic imaging in IDH-mutated glioma patients at 3.0 T in vivo

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TARGET AUDIENCE Neuro-oncologists, MR spectroscopists.

PURPOSE Isocitrate dehydrogenase mutations (IDH1 and IDH2) gives rise to a gain of function and produces oncometabolite 2-hydroxyglutarate (2HG) from α -ketoglutarate^{1,2,3}. Clinically, the presence of IDH mutations showed increased overall survival and longer transformation times compared with tumors expressing only the wild type of the enzyme^{1,2,3}. Recent studies have reported noninvasive detection of 2HG in gliomas MRS^{4,5,6}. To date studies have not been reported on the reproducibility of 2HG estimates, with single voxel or spectroscopic imaging (SI). We report first SI reproducibility study of 2HG measures. Preliminary data from five glioma patients are presented.

METHODS *MR experimental design:* Previously reported optimized PRESS TE of 97 ms ($TE_1 = 32$ ms and $TE_2 = 65$ ms)⁴ was used to acquire SI data on a Philips 3T whole-body scanner with 8-channel reception coil. Axial and sagittal T₂w-FLAIR images were acquired to localize the tumor region. All *in vivo* SI data were acquired with a TR of 1.2 sec, a spectral width of 2000 Hz, 1024 complex points per FID with two signal averages. Water signal was suppressed using a four-pulse scheme. The PRESS RF carrier was set to 2.6 ppm. The PRESS 90° and 180° pulses had bandwidths of 4.2 kHz (9.8 ms) and 1.3 kHz (13.2 ms), respectively. The VOI was positioned to cover most of the tumor region and some normal appearing brain region for comparison. Typically a 200 x 160 mm² field of view (FOV) in the phase encoding directions was used for acquisition with an in-plane resolution of 10 x 10 mm², and slice thickness of 15 mm along head-foot direction. Regional saturation bands were used to minimize extraneous signals from subcutaneous regions. The total scan time was 25 minutes. *Patient Population:* Five subjects with brain tumors were recruited for this study. Each subject had two MR examinations on the same day (Scan-1 and Scan-2) to evaluate the reproducibility. All the subjects had detectable 2HG signal. Written informed consent was obtained from subjects prior to the scans. *Post-processing:* Residual water signal in the metabolite data was removed using the HL-SVD filter of the JMRUI⁷. Frequency-drift and eddy current artifact corrections were performed using in-house Matlab programs. LCModel⁵ software was used for spectral fitting and estimation of metabolite concentrations. Basis-sets for LCModel were created from density matrix calculations¹ using published chemical shift and coupling constants^{9, 10}. The absolute quantification of the metabolites was performed using Cr signal in gray matter dominant region at 8 mM¹¹. *Reproducibility:* To evaluate the reproducibility, voxels from the tumor mass were selected and Coefficient of Variance (CV) and Intraclass Correlation Coefficient (ICC) were calculated with multifactorial random effects model from analysis of variance (ANOVA)^{12,13}.

RESULTS Figure 1 show a representative spectrum and various metabolite contributions from tumor region in subject with anaplastic oligoastrocytoma. The spectrum shows classical signs of tumor i.e. reduced N-acetylaspartic acid (NAA) and elevated choline (tCho). A large signal can be observed at 2.25 ppm which is primarily attributable to 2HG, which was estimated at 9.6 mM. The tCho and 2HG concentration maps correlate with the anatomical location of the tumor mass on T₂w-FLAIR. Figure 2 shows the Scan-1 and Scan-2 data from a subject with low grade oligodendroglioma. Spectra on the left and right were chosen from a normal appearing and tumor brain regions in the T₂w-FLAIR images, respectively. Spectra from Scan-1 (blue) are identical to the spectra from Scan-2 (brown), indicating excellent reproduction of the spectral pattern between the two scans. Figure 3 shows plots comparing the metabolite estimates from the Scan-1 to those from the Scan-2 for all five glioma subjects for 2HG, tCho, and tNAA. Mean 2HG levels over the tumor mass in five subjects were 3.1, 2.6, 3.2, 7.7 and 4.3 mM. The CV values for 2HG, tCho and tNAA were 0.29, 0.06 and 0.07, respectively. The ICC values for 2HG, tCho and tNAA were 0.77, 0.93 and 0.98, respectively. The ICC values for Glu and Gln were 0.84 and 0.81.

DISCUSSION AND CONCLUSION

The present work reports the first spectroscopic imaging reproducibility for 2HG, obtained using 2HG optimized PRESS TE = 97 ms⁴. The ICC values of tCho and tNAA are in agreement with prior healthy brain studies¹⁴. The ICC of 2HG was similar to ICC of Glu in prior studies⁴, indicating excellent reproducibility. However the CV of 2HG in the present study was ~3 fold larger than published values of Glu, most likely because of low concentration of 2HG compared to Glu levels in healthy brain (~4 mM vs 10 mM, respectively). Therefore we conclude that our data may show clinically acceptable reproducibility of 2HG and the SI method presented can provide a tool for monitoring 2HG changes in heterogeneous gliomas effectively.

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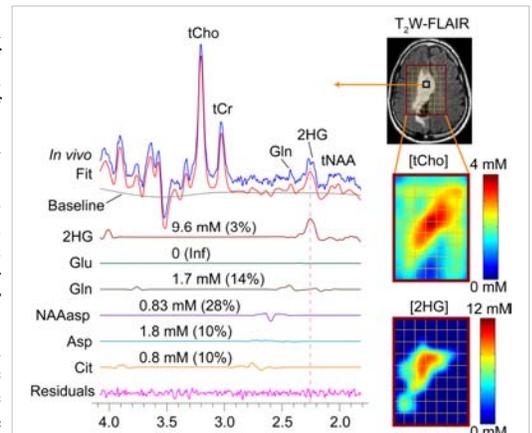


Fig. 1: *In vivo* spectroscopic imaging data from a subject with anaplastic oligoastrocytoma (Subject-4 in Fig 3). Spectra (blue), LCModel fit (red) and baseline (grey) along with metabolites signals with estimates and CRLB are shown.

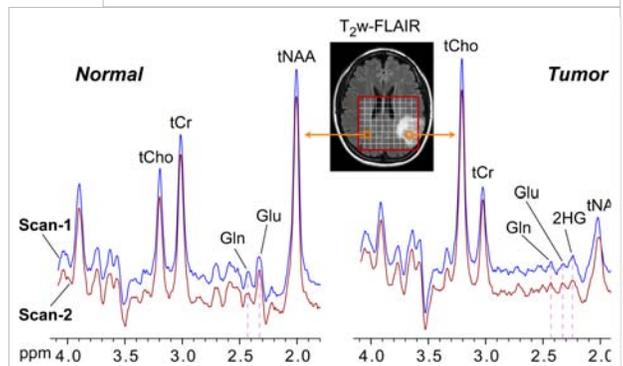


Fig. 2: *In vivo* spectroscopic Scan-1 and Scan-2 data from a low grade oligodendroglioma patient (Subject-3 in Fig 3). Spectra on the left and right were selected from the normal and tumor regions shown on the T₂w-FLAIR image. Spectra in blue and brown are from Scan-1 and Scan-2 respectively.

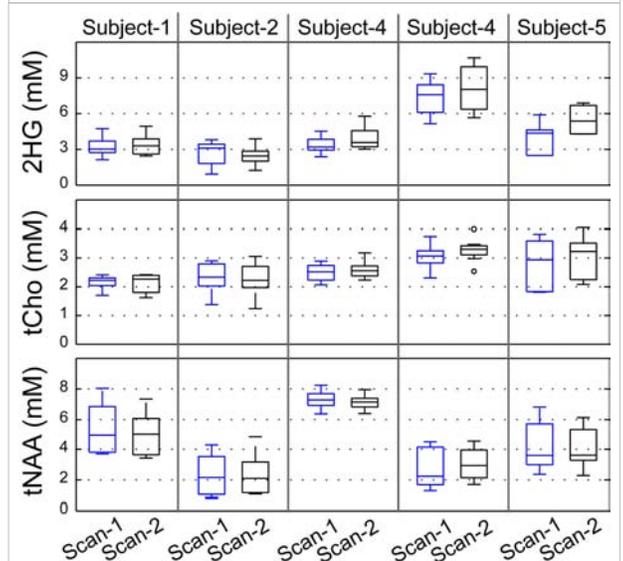


Fig. 3: Reproducibility plots of 2HG, tCho and tNAA in five subjects (axes are in mM) in Scan-1 and Scan-2.