Isotropic Diffusion Spectrum Imaging Constrained by Independent Component Analysis with a Ball and Stick Model to Assess Cellularity of Brain Tumors

JEONG-WON JEONG[1,2], Csaba Juhász[1,3], Sandeep Mittal[3,4], Edit Bosnyák[1], and Diane C Chugani[1,2]

[1]*Pediatrics and Neurology, Wayne State University, Detroit, MI, United States,* [2]*Children's Hospital of Michigan, Detroit, MI, United States,* [3]*Karmanos Cancer Institute, Detroit, MI, United States,* [4]*Neurosurgery and Oncology, Wayne State University, Detroit, MI, United States*

Targeted audience: Clinical researchers using diffusion tensor imaging in brain tumors. **Purpose**: Recently, an independent component analysis with ball-stick model (ICA+BSM)[1] was proposed to solve an intra-voxel crossing fiber problem in clinical diffusion tensor imaging (DTI) data, typically sampling the displacement of water diffusion at a q-space single shell with relatively low angular resolution (e.g., b-value =1000 s/mm^2 and number of encoding directions $\leq$ 15). The present study investigates whether the ICA+BSM analysis can be combined with isotropic diffusion spectrum imaging (IDSI) technique[2] in order to assess the degree of cellularity in tumor-infiltrated white matter tissues in clinical DTI applications. **Methods:** The present study included 7 patients presenting with histologically verified WHO grade II-IV gliomas. All MRI scans were performed on a 3T Philips scanner equipped with an eight-channel head coil. For IDSI, DTI data were gathered at repetition time (TR) = 10,870 ms, echo time (TE) = 108.9 ms, field of view (FOV) = 224 cm, 128 × 128 acquisition matrix, 2 mm thickness using 15 isotropic gradient directions with b-value = 1000 s/mm^2, one b = 0 acquisition, and number of excitations = 1. Apparent diffusion coefficient (ADC) images were acquired at 2 b-values of 0 and 1000 s/mm^2 with all other imaging parameters the same as described above for DTI. As a part of the clinical MRI protocol, conventional imaging sequences were acquired for pre- and post-contrast T1-weighted image and axial FLAIR image. To demarcate the proliferating tumor region in each patient, amino acid positron emission tomography (PET) using α[^{11}C]methyl-L-tryptophan (AMT)[3] was performed with 3.7 MBq/kg AMT tracer injection. AMT standardized uptake value (SUV) images were calculated by dividing the average tracer concentration in tissue at 30-55 min post-injection by the ratio of injected activity and patient weight. Regions with increased AMT-SUV in the lobes encompassing the tumor were defined as areas showing at least 36% higher AMT SUV as compared to mean AMT-SUV in contralateral cortex[3]. In high AMT uptake region, which is highly sensitive to differentiate actively proliferating glioma from necrotic regions, the number of crossing fibers (K_{opt} up to 3), fractional ratios ($f_{j=1,..,Kopt}$), and orientations of K_{opt}- crossing fibers ($e_{k=1,...,Kopt}$) were determined using ICA+BSM and then used to facilitate the numerical complexity of model selection and non-linear optimization to estimate isotropic diffusion spectrum ($f_{k=Kopt+1,.....,Kopt+L}$) in the jth-diffusion gradient measurement, $S_{j=1,2,...,15}(x,y,z)$: $S_j \cong \sum_{k=1}^{K_{opt}} f_k e^{-|\vec{b}_j|\lambda_{\perp k}} e^{-|\vec{b}_j|(\lambda_{\parallel k}-\lambda_{\perp k})\cos^2(\cos^{-1}\frac{r_j \cdot e_k}{|r_j||e_k|})} + \sum_{k=K_{opt+1}}^{K_{opt+L}} f_k e^{-|\vec{b}_j|d_k}$ where a set of parameters $\{e_k, K_{opt}\}$ was fixed in the overall fitting process. The fractions of anisotropic components,$\{f_{k=1,...,Kopt}\}$ were initialized by the solution of ICA+BSM and then optimized with other parameters: axial diffusivity of the k-th anisotropic component ($\lambda_{\parallel k}$), radial diffusivity of the k-th anisotropic component ($\lambda_{\perp k}$), a spectrum of isotropic components, $\{f_k=K_{opt+1},..,K_{opt+L}\}$ using generalized pattern search algorithm under the equality constraint of $\sum_{k=1}^{K_{opt+L}} f_k = 1$. d_k indicated the discrete value of isotropic diffusivity equally sampled at *L*-bins ranging from 0 to 0.0030 mm^2/s. The sum of total isotropic diffusion spectrum restricted from 0 to 0.0009 mm^2/sec was defined as cell ratio quantifying hypercellularity and compared with ADC value for the comparision. **Results:** Representative examples of AMT-SUV, T1-GAD, ADC, and IDSI-derived parameters including axonal loss ($\sum_{k=1}^{K_{opt}} \lambda_{\parallel k}/K_{opt}$), demyelination ($\sum_{k=1}^{K_{opt}} \lambda_{\perp k}/K_{opt}$), fiber ratio ($\sum_{k=1}^{K_{opt}} f_k$), cell ratio ($\sum_{d_k=0}^{d_k=0.0009} f_{d_k}$), and water ratio ($\sum_{d_k=0.0012}^{d_k=0.0030} f_{d_k}$) are shown in two glioblastoma (GBM) patients (**Fig. 1**). As marked by white arrows, the IDSI-derived cell ratio detected the cluster of voxels in the region showing increased AMT SUV and decreased ADC values of both GBM patients. Compared with ADC, which provided a moderate accuracy of 0.457 to detect proliferating tumor cells in the active tumor region, IDSI-derived cell ratio yielded a much higher accuracy of 0.969 in conventional receiver operating characteristic curve analysis performed in the seven grade II-Iv gliomas. **Discussion and Conclusion**: By combining AMT-PET with IDSI-MRI to measure restricted isotropic diffusivity in the framework of ICA+BSM, the present study demonstrates the potential clinical use of a new, refined imaging tool to evaluate the degree of cellularity associated with brain tumor proliferation.

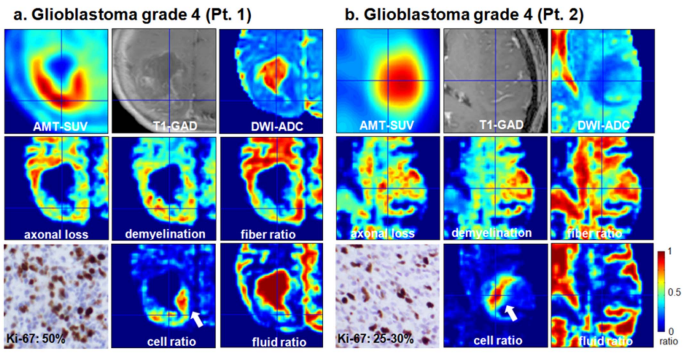

Figure 1. Results of AMT-PET, T1-GAD, ADC, axonal loss ($\sum_{k=1}^{K_{opt}} \lambda_{||k}/K_{opt}$), demyelination ($\sum_{k=1}^{K_{opt}} \lambda_{\perp k}/K_{opt}$), fiber ratio ($\sum_{k=1}^{K_{opt}} f_k$), Ki-67 cell labeling, cell ratio ($\sum_{d_k=0}^{d_k=0.0009} f_{d_k}$), and water ratio ($\sum_{d_k=0.0012}^{d_k=0.0030} f_{d_k}$) for two GBM grade 4 patients.

References: 1. Jeong JW, Asano E, Yeh FC, et al. Independent component analysis tractography combined with a ball-stick model to isolate intra-voxel crossing fibers of the corticospinal tracts in clinical diffusion MRI. Magn Reson Med. 2013;70:441–53. 2. Wang Y, Wang Q, Haldar JP, et al. Quantification of increased cellularity during inflammatory demyelination. Brain 2011;134(Pt12):3590-601. 3. Juhasz C, Chugani DC, Muzik O, et al. In vivo uptake and metabolism of alpha-[^{11}C]methyl-L-tryptophan in human brain tumors. J Cereb Blood Flow Metab. 2006; 26(3):345-57. 4. Kamson DO, Mittal S, Robinette NL, et al. Increased tryptophan uptake on PET has strong independent prognostic value in patients with a previously treated high-grade glioma. Neuro Oncol. 2014 Apr 1. doi: 10.1093/neuonc/nou042.