Detection of Brain Tumor Invasion

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Synopsis: The stretched exponential model of diffusion-related signal decay in MRI was developed to account for changes in heterogeneity accompanying C6 glioma invasion in rats. The model is preferred to the bi-exponential model, because there is no *a priori* information about the diffusion values present. Six rats were inoculated with tumor cells and imaged 14-15 days later. Sub-voxel (0.5mm×0.5mm×1mm) heterogeneity, as measured by the model, increased in tumor-inoculated rats in regions of contrast enhancement. Second and third moments of the diffusion distribution increased in a region inferior to the contrast –enhanced area, possibly delineating regions of latent tumor cell invasion.

Introduction: The most difficult aspect of treating high-grade gliomas is that they have infiltrated the normal brain before they can be seen. It is the undetected invasion of tumors cells into surrounding normal tissue that is blamed for the failure of all conventional brain tumor treatments, with mean survival rates ranging from only a few months to a few years. Consequently, a noninvasive means to detect tumor invasion would have a profound impact on the evaluation and treatment of these patients. In this regard, we are developing a method of diffusion-weighted image (DWI) analysis that is sensitive to intra-voxel diffusion heterogeneity as a marker of extra-cellular matrix (ECM) breakdown. The ECM breakdown is a necessary step in the tumor invasion process.

Our approach was to apply the stretched-exponential model (1,2) to the DWI signal attenuation (S/S_0) as a function of diffusion weighting factor b, with a fitted "distributed diffusion coefficient" **DDC** and "stretching parameter" **α.** The parameter α is a homogeneity index. It has a value of 1 if diffusion is mono-exponential, and is reduced if more diffusion components are present**.** The model is written as:

$$S/S_0 = \exp\{-(b\times DDC)^{\alpha}\}. \qquad (1)$$

Using both **DDC** and **α,** it can be shown that the nth moment $E(D^n)$ of the intra-voxel distribution of diffusion coefficients (D) is given by the relationship:

$$E(D^n) = (DDC/\alpha)(\Gamma(n/a)/\Gamma(n)). \qquad (2)$$

Both $E(D^n)$ and α are measures of sub-voxel heterogeneity in the distribution of diffusion coefficients, with a high $E(D^3)$ indicating that heterogeneity is a result of intra-voxel diffusion components which are much lower or higher than the mean value $E(D^1)$.

Methods: Six male Sprague-Dawley rats were inoculated with 10^5 (10μl) human C6 glioma cells. Cells were injected at a depth of 3 mm from the dural surface. Rats were imaged 14-15 days after tumor inoculation. Six healthy Sprague-Dawley rats were imaged as a control. The rats were anesthetized using urethane (1.2 g/kg), with 0.1 ml booster injections as needed, and were immobilized with a fiberglass bite bar. Rats were imaged on a Bruker Biospec 3T spectrometer using a Stejskal-Tanner pulse sequence with a 64×64 matrix, a FOV of 6.4 cm, an axial slice thickness of 1.0 mm, and a TE of 43 ms. The b-value was varied from 0 to 6500 s/mm^2 in increments of 500 s/mm^2, with a diffusion time of 27 ms, and b-values were applied in a random order in the read-gradient direction. Two averages were obtained for each b-value. Rats were given an injection of gadopentate (Magnevist) following the DWI, and T1-weighted images were acquired. The DWI data was fit with the stretched-exponential model (Eq. 1) on a voxel-wise basis, using a nonlinear least-squares simplex algorithm.

Results: Mean α values were $0.88 \pm 1\times10^{-3}$ and $0.92\pm2.2\times10^{-5}$ in the tumor and control rats, respectively, with significantly lower ($p<0.001$) α in the voxels from the Gd-enhancing ROI of the rats with tumors, seen in Fig. 1. Figs. 2 and 3 show maps of the stretched exponential fits of data from one representative tumor (Fig. 2) and one control (Fig. 3) rat. The color bar, indicating relative signal intensity, is shown on the far right. As seen in Fig. 2, color maps in all six rats contained a region of high **DDC** below the area of contrast enhancement, as well as successively larger areas of high values in the moments of the distribution of **D**. The images of healthy brain with an equivalent slice showed only **DDC** and $\mathbf{E(D^n)}$ enhancement in white matter (corpus callosum), but the contrast was not visible directly below the corpus callosum in the image.

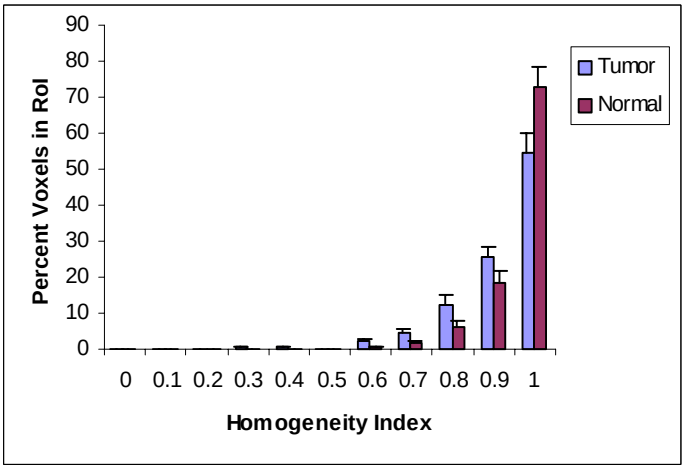

Fig.1: *Histogram of homogeneity index (α) in voxels from six healthy and six tumor-inoculated rats. Inter-rat standard deviations are shown.*

Conclusions: This, to our knowledge, is the first report of increased sub-voxel heterogeneity in diffusion rates with no spatially-corresponding enhancement in local post-contrast images, suggesting that this technique may be a new marker of tumor invasion. Other sources of such signal change seem unlikely. For example, the T2-weighted images (b=0) did not show enhancement in the regions of enhanced moments of **D**, (and particularly $E(D^3)$), rejecting edema as the source of high diffusion contrast. The pre-Gd T1 images were unenhanced in these areas, making local infarction and blood leakage unlikely as a source of the observed changes. Acute infarction has been shown to cause iso-intense T1 maps, but it is unlikely that such infarction occurs in every rat just hours before imaging. (If infarction occurred earlier, for instance, T1 should increase). The changes may be due to physical deformation of white matter by the tumor or to cellular changes predating invasion into white matter by the glioma cells.

References:

1. K.M. Bennett, J.S. Hyde, and K.M. Schmainda. ISMRM Workshop on Functional and Assessment of Cancer. 2002. **2.** Benny Lee KC, Siegel J, Web SED, Leveque-Fort S, Cole MJ, Jones R, Dowling K, Lever MJ, and French PMW**.** *Biophys J* 2001, 81:1265-1274.

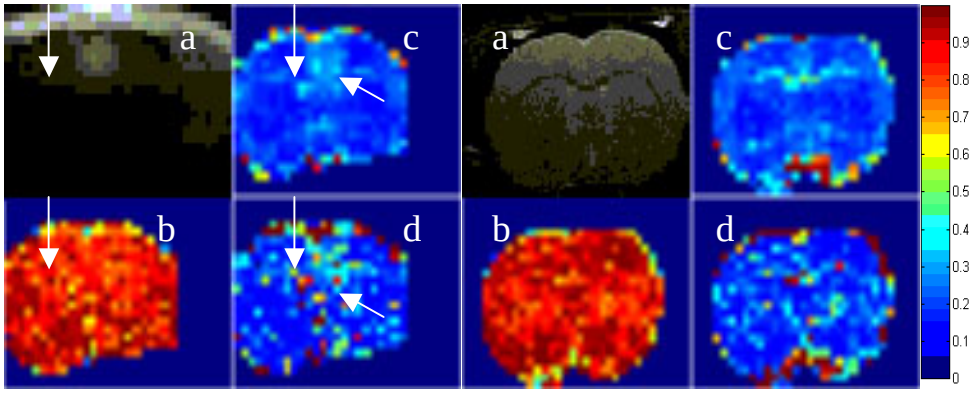

Fig 2: *Maps of Stretched-Exponential parameters in C6 glioma inoculated rats. Labels are as follows: a. Post-Gd T1-weighted image, b. Map of α, c. Map of DDC, d. $E(D^3)$ maps. Vertical arrows indicate the depth of contrast enhancement, and diagonal arrows indicate the region of observed diffusion changes.*

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