Intravoxel water diffusion heterogeneity of human high-grade gliomas

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Introduction
Diffusion-weighted signal decay of brain tissue is known to be multi-exponential due to the presence of multiple proton pools with different diffusion coefficients inside each voxel [1]. However, the number of distinct proton pools in each voxel is unknown and there is no consensus about the most suitable model to fit diffusion-weighted signal attenuation curves. Recently, the stretched-exponential model was introduced, which does not make any assumption about the number of intravoxel proton pools contributing to diffusion-weighted signal decay [2]. Besides a distributed diffusion coefficient (DDC), a quantification of intravoxel distribution of apparent diffusion coefficients, this model also allows calculation of a diffusion heterogeneity index (), which reflects the heterogeneity of intravoxel water diffusion rates [2]. The purpose of this study was to apply the stretched-exponential model to high-grade gliomas, and to obtain baseline diffusion heterogeneity indices of anatomic landmarks and tumor as prerequisites to therapy response studies.

Materials and Methods
Institutional review board approval and written informed consent were obtained. Twenty high-grade glioma patients (WHO grade III: 3, WHO grade IV: 17, 10 men, 10 women, mean age 58.2 years [range, 20-89 years]) underwent pretherapy (baseline) anatomic and diffusion-weighted MR imaging (DWI), using a 3.0-T system (Gyrosan Achieva; Philips Healthcare, Best, the Netherlands) with an eight-channel head coil. Trace DWI was performed at b-values of 0, 1000, 2000, and 4000 s/mm2, using a SS-EPI sequence (TR/TE 8700/60 ms) with parallel imaging (SENSE factor = 3). Whole brain isotropic DWI at 23 mm resolution was obtained in 4′30″. The stretched-exponential model is described as follows: \( S(b) = \exp(-(b \times DDC)^\alpha) \), where \( S(b) \) is the signal magnitude with diffusion weighting \( b \), and \( S_0 \) is the signal magnitude with no diffusion weighting [2]. The parameter \( \alpha \) is the diffusion heterogeneity index, varying between 0 and 1, and the DDC is the distributed diffusion coefficient. An \( \alpha \) near 1 indicates a mono-exponential decay, whereas an \( \alpha \) near 0 indicates stronger multi-exponential decay [2]. The stretched-exponential model was fitted to the acquired DWI data to create pixel-by-pixel and DDC maps, using a nonlinear least squares routine in Matlab (The Mathworks, Inc.). Noise thresholds were set to restrict diffusion calculation to only pixels safely above background noise to avoid fitting voxels with low signal-to-noise ratio. Regions of interest were placed in the tumor and in four contralateral anatomic landmarks (frontal white matter, basal ganglia, cortical grey matter, and centrum semiovale), and corresponding \( \alpha \) and DDC values were calculated. Differences between mean \( \alpha \) of tumors and mean \( \alpha \) of landmark tissues were assessed using paired \( t \) tests. Correlation between tumor \( \alpha \) and tumor DDC was assessed using Pearson’s correlation coefficient (0: no correlation, (-1): perfect correlation). \( P \) values < 0.05 were considered statistically significant.

Results
Results are displayed in Table 1. Mean \( \alpha \) of tumors was significantly lower than mean \( \alpha \) of contralateral frontal white matter \( (P = 0.0249) \), basal ganglia \( (P < 0.0001) \), cortical grey matter \( (P = 0.0097) \), and centrum semiovale \( (P = 0.0097) \). Mean DDC of tumors was significantly higher than mean DDC of contralateral frontal white matter \( (P = 0.0001) \), basal ganglia \( (P < 0.0001) \), cortical grey matter \( (P < 0.0001) \), and centrum semiovale \( (P < 0.0001) \). Figure 1 demonstrated the correlation between tumor \( \alpha \) and tumor DDC, which was strongly negative \( (r = -0.8493; P < 0.0001) \). Figure 2 shows a representative example of \( \alpha \) and DDC maps of a high-grade glioma.

Table 1. Mean ± SD \( \alpha \) and DDC (in 10^-3 mm^2/s) of different structures and tumor.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>( \alpha )</th>
<th>DDC</th>
</tr>
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<tbody>
<tr>
<td>Frontal white matter</td>
<td>0.62 ± 0.01</td>
<td>0.80 ± 0.09</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>0.80 ± 0.03</td>
<td>0.64 ± 0.05</td>
</tr>
<tr>
<td>Cortical grey matter</td>
<td>0.72 ± 0.03</td>
<td>0.72 ± 0.04</td>
</tr>
<tr>
<td>Centrum semiovale</td>
<td>0.62 ± 0.02</td>
<td>0.70 ± 0.05</td>
</tr>
<tr>
<td>Tumor</td>
<td>0.58 ± 0.08</td>
<td>1.64 ± 0.71</td>
</tr>
</tbody>
</table>

Figure 1. Scatter plot with tumor \( \alpha \) (x-axis) vs. tumor DDC (y-axis), including regression line and 95% confidence interval.

Figure 2. Representative case of a high-grade glioma (WHO grade III) in the left temporal lobe with high DDC and low \( \alpha \). Note that the apparent “zero” DDC and \( \alpha \) values in the CSF and cyst are only a result of noise thresholding – these pixels were not included in the analyses.

Conclusions
This study indicates that heterogeneity of intravoxel water diffusion rates is significantly higher in high-grade gliomas than in normal brain tissue, which potentially offers a new method for assessing tumor extent and for evaluating therapeutic response in high-grade gliomas. Furthermore, the strong negative correlation between tumor \( \alpha \) and tumor DDC suggests that highly cellular tumors contain a lower number of distinct intravoxel proton pools, while cystic or necrotic tumors contain a higher number of distinct intravoxel proton pools.

References