Anomalous Diffusion in Cerebral Glioma Assessed Using a Fractional Motion Model

Boyan Xu,1,2 Lu Su,3 Zhenxiong Wang,4 Yang Fan,5 Gaolang Gong,6 Wenzhen Zhu,4 Peiyi Gao,3 and Jia-Hong Gao1,2,7*

Purpose: To demonstrate the capability of the fractional motion (FM) model for describing anomalous diffusion in cerebral gliomas and to assess the potential feasibility of FM for grading these tumors.

Methods: Diffusion MRI images were acquired from brain tumor patients using a special Stejskal-Tanner diffusion sequence with variable diffusion gradient amplitudes and separation times. Patients with histopathologically confirmed gliomas, including astrocytic and oligoastrocytic tumors, were selected. The FM-related parameters, including the Noah exponent (α), the Hurst exponent (H), and the memory parameter (μ = H – 1/α), were calculated and compared between low- and high-grade gliomas using a two-sample t-test. The grading performance was evaluated using the receiver operating characteristic analysis.

Results: Twenty-two patients were included in the present study. The calculated α, H, and μ permitted the separation of tumor lesions from surrounding normal tissues in parameter maps and helped differentiate glioma grades. Moreover, α showed greater sensitivity and specificity in distinguishing low- and high-grade gliomas compared with the apparent diffusion coefficient (ADC).

Conclusion: The FM model could improve the diagnostic accuracy in differentiating low- and high-grade gliomas. This improved diffusion model may facilitate future studies of neuro-pathological changes in clinical populations. Magn Reson Med 000:000–000, 2017. © 2017 International Society for Magnetic Resonance in Medicine.

Key words: anomalous diffusion; high b-value diffusion imaging; cerebral glioma

INTRODUCTION

Diffusion MRI (dMRI) has become a pillar of modern clinical imaging and is being incorporated into general oncologic imaging practice (1,2). Compared with other MRI modalities, dMRI probes the diffusion process in tissues at the cellular scale (e.g., micrometers), well beyond the typical millimetric image resolution (3). The observation of water diffusion in vivo provides unique information about the microscopic properties of biological tissues. Therefore, dMRI has great potential to become a cancer biomarker (2,4). Its clinical applications include characterizing the tumor malignancy, monitoring treatment response, differentiating posttherapeutic changes from residual active tumors and detecting recurrent cancer (2). For example, the most widely used dMRI parameter, the apparent diffusion coefficient (ADC), was found useful in the differentiation of some human brain tumors (5) and tumor grading (6). dMRI is most frequently acquired with b-values ranging from 0 to 1000 s/mm² and is quantified using the mono-exponential model, $S/S_0 = \exp(-b \cdot \text{ADC})$, which assumes a normal diffusion process in biological tissues. However, numerous experiments have shown that the observed dMRI signal decay curve deviates from the mono-exponential form in biological tissues, particularly over an extended b-value range (7). To address this problem, several models have been developed to find an optimal agreement between the experimental data and the proposed fitting curves. These models include the bi-exponential model (8,9), the stretched exponential model (10), the statistical model (11), and the kurtosis model (12). In addition to these empirical mathematical models, researchers have also attempted to explain the deviation of signal attenuation through anomalous diffusion processes. Several physics-motivated dMRI models have been proposed based on different theories for various anomalous diffusion processes (13–18). The parameters derived from these models enable a more detailed investigation of differences between tumor types and grades (19–25).

Notably, several studies have indicated that the fractional motion (FM) model is a more appropriate method to describe the diffusion process in living cells (26–30). FM assumes that the diffusion process is $\alpha$-stable, $H$-self-similar, and has stationary increments (31). The symbol $\alpha$ denotes the Noah exponent, which quantifies the fluctuations of the random process. The increments are Gaussian distributed when $\alpha = 2$, while the increments are Lévy distributed when $0 < \alpha < 2$. $H$ is the Hurst exponent that describes the self-similarity property of molecular trajectories. The increments of the process are positively correlated and exhibit long-range dependence (long memory, persistence) when the memory parameter is $\mu = H – 1/\alpha > 0$. However, for $\mu < 0$, the increments are negatively correlated and exhibit short-range dependence (short memory, anti-persistence) (28). In the case of $\mu < 0$, the diffusion process...
follows a subdiffusive pattern (28), which has been observed in living cells (32).

The FM-based dMRI theory has only recently been proposed, and the spatially resolved FM-related parameter maps of healthy volunteers have been obtained, showing remarkable contrasts among normal brain tissues (18). However, the FM model has not yet been applied to any brain diseases. The assessment of the relationship between the parameters (α, H and μ) of the FM model and tumor histopathology would enable the detection of differences among tumor types and grades with high sensitivity. In this note, the FM model was investigated in cerebral gliomas, the most common type of primary brain tumor. The purpose of the present study was to evaluate the potential value of the FM model in differentiating grades of gliomas.

METHODS

Patients

This study was approved by the local institutional review board and was performed in compliance with the Health Insurance Portability and Accountability Act. Informed consent was obtained from all participants. A total of 50 adult patients with brain tumors underwent MRI examination. Patients were selected if they met the following criteria: (a) MR imaging was performed before the treatment of tumors; (b) patient had no concurrent brain diseases unrelated to the tumor; and (c) a histopathological diagnosis of glioma was assigned after surgical resection.

Image Acquisition

MR imaging was performed on a 3 Tesla (T) GE Discovery MR750 MRI scanner (GE Healthcare, Milwaukee, Wisconsin) equipped with an eight-channel head coil. All dMRI images were obtained using a special Stejskal-Tanner single-shot spin-echo echo-planar-imaging sequence. To fit the FM model, the diffusion gradient separation time (Δ) was not fixed during the scanning process as the conventional dMRI sequence. Specifically, Δ was set at 27.5, 40.0, and 55.5 ms. For each Δ value, the diffusion gradient amplitude (G0) was set at 15.67, 19.68, 24.73, 31.06, 39.01, and 49.00 mT/m, which were chosen to be approximately evenly spaced on a log axis. The gradient duration constant (δ) was kept constant (20.4 ms). Therefore, a total of 18 nonzero b-values were produced in each gradient direction (151, 239, 377, 595, 938, 1480, 243, 383, 604, 954, 1504, 2374, 356, 562, 887, 1399, 2207, and 3482 s/mm²). The diffusion gradients were successively applied in three orthogonal directions (the x-axis, y-axis, and z-axis) to minimize the effect of diffusion anisotropy. In addition, a total of 12 images without diffusion sensitization (b = 0) were obtained. The other data acquisition parameters for this diffusion sequence were: TR/TE = 3800 ms/110 ms; accelerating factor = 2; field-of-view = 24 cm × 24 cm; matrix size = 128 × 128; slice thickness = 5 mm; and number of excitations = 2. The total scan time was 8 min and 42 s to facilitate clinical use. In addition, routine MRI examinations were performed, including gadolinium contrast-enhanced T1-weighted imaging and T2-weighted imaging.

Image Analysis

Before image analysis, the acquired images were corrected for eddy current distortions and head motions using FSL tools (33). ADC maps were calculated using the images acquired at b-values of 0 and 954 s/mm². To obtain the anomalous diffusion parameters, the images were analyzed using the FM model. According to the FM-based dMRI theory (18), the diffusion induced signal decay can be formulated as

$$S/S_0 = \exp(-D_{an} H b_{an})$$

where $D_{an}$ is the generalized diffusion coefficient of anomalous diffusion, and $b_{an}$ is the generalized b-value. When using the Stejskal-Tanner diffusion sequence (34), this generalized b-value can be calculated as

$$b_{an} = \eta \cdot \gamma^2 G_0^2 \Delta^{n+\alpha} H$$

where γ is the gyromagnetic ratio. As mentioned above, $G_0$ is the diffusion gradient amplitude, and Δ is the gradient separation time. In Equation [2], η is a dimensionless number, which can be calculated using the formula

$$\eta = \frac{1}{(1 + \mu)^\alpha} \int_0^{b/\Delta} \left( \frac{\delta}{\Delta} + 1 - u \right)^{1+\mu} - (1 - u)^{1+\mu} - \left( \frac{\delta}{\Delta} - u \right)^{1+\mu} \left( \alpha + \alpha \right) \left( \alpha \right) du$$

The signal attenuation at each voxel was fitted to Equation [1] separately along each direction. Directionally averaged maps were subsequently calculated to reduce the influence of anisotropy. All fitting procedures were performed using the trust-region-reflective nonlinear fitting algorithm in Matlab (MathWorks, Natick, MA).

Two radiologists (Z.W., L.S.) who were in consensus manually drew the region of interest (ROI) for tumor and normal-appearing white matter (NAWM) on the T2-weighted echo-planar images (i.e., the dMRI images with b-values of 0 s/mm²) according to the contrast-enhanced T1-weighted images and T2-weighted images. The selected tumor ROIs included only the solid region of the tumor, despite enhancement. The NAWM ROI was drawn in contralateral normal-appearing white matter (NAWM) on the T2-weighed images and T2-weighted images. The tumors were blinded to all parameter maps. Subsequently, the mean values of the estimated ADC, α, H, and μ were calculated
over the selected ROIs. To objectively quantify tumor conspicuity, the relative parameters (ADC<sub>r</sub>, α<sub>r</sub>, H<sub>r</sub>, and μ<sub>r</sub>) were generated by dividing the mean value in tumor ROI by the mean value in the corresponding NAWM.

To assess the feasibility of the FM model for tumor grading, the mean values for ADC, α, H, and μ of the tumor ROIs and the relative parameters to the contralateral NAWM were compared among high- and low-grade gliomas using a two-sample t-test. A probability of less than 5% (P-values < 0.05) was considered statistically significant. Moreover, to quantify the overall sensitivity and specificity of these parameters in differentiating low- and high-grade gliomas, receiver operating characteristic (ROC) curves were generated to assess the area under the curve (AUC).

**RESULTS**

Overall, 22 patients were included in the present study (15 males and 7 females; mean age, 43.0 years; age range, 25–60 years). According to the World Health Organization (WHO) criteria (35), this patient group comprised 16 astrocytic tumors (4 WHO grade II, 1 WHO grade III, and 11 WHO grade IV) and 6 oligoastrocytic tumors (2 WHO grade II and 4 WHO grade III). The patients were divided into low-grade (WHO grade I or II; n = 6; 1 female; mean age, 40.5 years; age range, 31–60 years) and high-grade (WHO grade III or IV; n = 16; 6 females; mean age, 43.9 years; age range, 25–59 years) tumor groups.

To evaluate the fitting procedures in the tumor regions, the mean values of the fitting residuals over both tumor and contralateral NAWM ROIs were calculated. The results of the paired t-test showed that the mean fitting residuals of tumor ROIs were significantly lower than those of the contralateral NAWM ROIs (P-values < 0.001) indicating that the FM-model matches the tumor data well.

Representative imaging results for this patient group are shown in Figure 1. The directionally averaged maps of the FM-related parameters (α, H, and μ), contrast-enhanced T<sub>1</sub>-weighted images, the T<sub>2</sub>-weighted images and the directionally averaged ADC maps are shown. On the α, H, and μ maps, the contrast of normal gray matter/white matter/cerebrospinal fluid in the FM-related parameter maps was similar to the contrast depicted in a previous study involving healthy subjects (18). On the other hand, the α, H, and μ maps showed a clear distinction of tumor lesions and peritumoral edemas from normal tissues.

The mean values of the parameters in both tumor and NAWM ROIs are summarized in Table 1. Figure 2 displays scatter diagrams of α versus H and μ. Together with the mean values for all tumor ROIs, the relative parameters were also plotted to eliminate the individual difference effect. As Figure 2 depicts, the brain tumor and NAWM can be readily separated using α, H, and μ, even when these parameters of tumor ROIs widely varied. Moreover, Figure 2 demonstrates the separation between high- and low-grade gliomas based on FM-related parameters. Significant differences were observed between high- and low-gliomas for the mean α (P-value < 0.0001), μ (P-value < 0.01), and ADC (P-value < 0.05), whereas H (P-value = 0.48) failed to differentiate between high- and low-grade gliomas. The same results were obtained using the relative parameters, where α, μ, and ADC succeeded in differentiating high- and low-grade gliomas (P-value < 0.001 for α, P-value < 0.05 for μ, and P-value < 0.05 for ADC), but H failed to differentiate these tumors (P-value = 0.40).

The performance in differentiating low-grade and high-grade gliomas was also illustrated in the ROC analysis. Figures 3a,b display the ROC curves calculated from the mean and relative values, respectively, for all tumors. Although influenced by the limited number of cases, larger AUCs were obtained with α (AUC = 0.98 in Figure 3a, AUC = 0.96 in Figure 3b) and μ (AUC = 0.99 in Figure 3a, AUC = 0.84 in Figure 3b) compared with ADC (AUC = 0.83 in Figure 3a, AUC = 0.88 in Figure 3b); H exhibited the smallest AUC (AUC = 0.59 in Figure 3a,
AUC = 0.64 in Figure 3b). For α, the highest Youden index (sum of sensitivity and specificity minus one) was reached when 1.70 ≤ α ≤ 1.73, while the optimal threshold for μ was between -0.077 and -0.073. Moreover, αr in range from 1.16 to 1.19 maximized the Youden index. These findings suggest the potential feasibility of FM-related parameters, particularly α, in distinguishing between low- and high-grade gliomas.

**DISCUSSION**

In the present study, the FM model was applied to analyze anomalous diffusion in tumor lesions in vivo. The FM-related parameters exhibited remarkable image contrasts that related to the anomalous diffusion, which were different from ADC. Although it is difficult to fully clarify the relationship between FM-related parameters and tumor characteristics from the limited number of patients included in the present study, these parameters were useful for differentiating low- and high-grade gliomas. Notably, α provides a higher sensitivity and specificity than the most commonly used diffusion parameter, ADC, for grading gliomas. Additional studies using a large population would increase the statistical power for sounder conclusions.

The FM-related parameter values in gliomas, particularly high-grade gliomas, varied over a large range. In addition to the differences in types and grades, this phenomenon can result from several causes. High-grade tumors are histologically heterogeneous (36,37), influenced by tumor cellularity, nuclear atypia, pleomorphism, and nuclear-to-cytoplasmic ratio. Other components may also contribute to this phenomenon, including necroses, cysts, and tortuous vascular hyperplasia within tumor matrix (36,38,39). Taken together, these factors diversify the microstructure of histologic tissue and lead to variations in FM-related parameters.

As shown in Equation [2], α is an exponent of the diffusion gradient that is mathematically proportional to

![Graph](image)

**FIG. 2.** Scatter diagrams of α versus H and μ. Both the mean values for all tumor ROIs (a,b) and the relative parameters to contralateral normal-appearing white matter (NAWM) (c,d) are plotted. All gliomas are classified according to type and grade. The parameter values for the NAWM regions are displayed for reference.
the parameters proposed by other dMRI models, such as the stretching parameter in the stretched-exponential model (10,16,40). These parameters are consistent with the $\alpha$ in gray matter, white matter, and cerebrospinal fluid, indicating that the calculation of FM-related parameters is reliable. While these parameters have been explained as an index of heterogeneity in water diffusion, $\alpha$ describes the variances of increments of diffusion processes according to the FM theory (18,31). To fully clarify the relationship between the imaging parameters and pathological changes, the precise diffusion process in tumor tissue should be further explored.

The limitations of the present study must be acknowledged. First, the use of single-shot echo-planar imaging may lead to image distortion and signal loss. Although these artifacts have been considerably reduced as a result of the development of high-performance gradients and parallel imaging, they may still occur, and the evaluation of the tumors in these areas may be confined. Second, the voxel was large, and a single voxel depicted an aggregated measure of the neuronal environment for a large sample size, which may hamper sensitivity to tissue components occupying a small fraction of a voxel. Another limitation is the sampling bias of the ROIs as a result of tissue heterogeneity. The direct voxel-wise radiobiologic-pathologic correlation should be further explored.

Notably, diffusion in brain tissue is known to be directionally dependent, that is, anisotropic. Diffusion tensor imaging is the most commonly used approach to describe diffusion anisotropy in tissue. With maps showing anisotropy, tumor growth-related changes in white matter, such as tumor infiltration or invasion, can be observed (41). Moreover, advanced models that characterize diffusion anisotropy could improve the delineation of tumors from NAWM (42). With anisotropy considered, the FM model may offer improved clinical utility. A study of the anisotropy of the parameter maps of the FM model is currently under way.

CONCLUSIONS

In summary, the FM model was successfully applied in cerebral glioma cases, and the results indicated that the anomalous diffusion parameter images could assist in grading gliomas. The utility of this model may lead to a new perspective on investigating pathological changes in tissues.

ACKNOWLEDGMENTS

B.X., L.S., and Z.W. contributed equally to this work.

REFERENCES