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Original contribution

Anisotropy of anomalous diffusion improves the accuracy of differentiating low- and high-grade cerebral gliomas

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ABSTRACT

Background: Anomalous diffusion model has been introduced and shown to be beneficial in clinical applications. However, only the directionally averaged values of anomalous diffusion parameters were investigated, and the anisotropy of anomalous diffusion remains unexplored. The aim of this study was to demonstrate the feasibility of using anisotropy of anomalous diffusion for differentiating low- and high-grade cerebral gliomas.

Methods: Diffusion MRI images were acquired from brain tumor patients and analyzed using the fractional motion (FM) model. Twenty-two patients with histopathologically confirmed gliomas were selected. An anisotropy metric for the FM-related parameters, including the Noah exponent (α) and the Hurst exponent (H), was introduced and their values were statistically compared between the low- and high-grade gliomas. Additionally, multivariate logistic regression analysis was performed to assess the combination of the anisotropy metric and the directionally averaged value for each parameter. The diagnostic performances for grading gliomas were evaluated using a receiver operating characteristic (ROC) analysis.

Results: The Hurst exponent H was more anisotropic in high-grade than in low-grade gliomas ($P = 0.015$), while no significant difference was observed for the anisotropy of α. The ROC analysis revealed that larger areas under the ROC curves were produced for the combination of α (1) and the combination of H (0.813) compared with the directionally averaged α (0.979) and H (0.594), indicating an improved performance for tumor differentiation.

Conclusion: The anisotropy of anomalous diffusion can provide distinctive information and benefit the differentiation of low- and high-grade gliomas. The utility of anisotropic anomalous diffusion may have an improved effect for investigating pathological changes in tissues.

1. Introduction

Diffusion MRI (dMRI) has become a pillar of modern clinical imaging and is being incorporated into general oncologic imaging practice [1–3]. Compared with other MRI modalities, dMRI probes the diffusion process in tissues at the cellular scale (e.g., micrometers), which is well beyond the typical millimetric image resolution [4]. The observation of water diffusion in vivo provides unique information about the microscopic properties of biological tissues. One of the most essential microscopic properties in the nervous system obtained by dMRI is directionally dependence (i.e., anisotropy), which mainly occurs due to the dense packing of axons and the inherent axonal membranes that hinder water diffusion perpendicular to the long axis of fibers relative to the preferential parallel direction [5]. The most commonly used method to measure anisotropy is diffusion tensor imaging (DTI) [6,7]. DTI models the molecular displacement in tissues with a three-

Abbreviations: ADC, apparent diffusion coefficient; AUC, area under the curve; dMRI, diffusion MRI; DTI, diffusion tensor imaging; FA, fractional anisotropy; FM, fractional motion; gFA, generalized fractional anisotropy; NAWM, normal-appearing white matter; ROC, receiver operating characteristic; ROI, region of interest; WHO, World Health Organization

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dimension Gaussian ellipsoid, which can be expressed as a symmetric positive semidefinite tensor. The fractional anisotropy (FA), which is calculated from the eigenvalues of the diffusion tensor, is the most widely used metric to describe the degree of anisotropy and has been widely applied in clinical research [1–3,8–11].

DTI is based on the regular diffusion model, which regards diffusion in biological tissues as a normal diffusion process and, thus, relates signal attenuation to the apparent diffusion coefficient (ADC) in the mono-exponential form $S/S_0 = \exp(-b \cdot \mathrm{ADC})$. The b-value characterizes the applied magnetic field gradient sequence. However, numerous experiments have shown that the observed dMRI signal decay curve deviates from the mono-exponential form in biological tissues, particularly over a high b-value range [12]. Additionally, the observed diffusion-time dependence of the MR signal reflects the non-Gaussian nature of diffusion [13]. To address this issue, several models have been developed, including the bi-exponential model [14,15], the stretched exponential model [16], the statistical model [17] and the kurtosis model [18]. In addition to these empirical mathematical models, several physics-motivated dMRI models have also been proposed based on different theories of anomalous diffusion processes [19–24].

The clinical feasibility of anomalous diffusion in dMRI has been demonstrated [25–31]. In these studies, the anomalous diffusion parameter values acquired with different gradient directions were averaged, and the effect of anisotropy was ignored. Several laboratories including ourselves have recently found that the anisotropy of anomalous diffusion is non-negligible and exhibits different image contrast compared with conventional DTI [32–35]. However, the clinical feasibility of utilizing the directional information from anomalous diffusion remains unexplored.

The aim of this study was to investigate whether the anisotropy of anomalous diffusion can play a role in the differentiation of low- and high-grade cerebral gliomas. In this research, dMRI images were acquired from cerebral glioma patients and analyzed using the fractional motion (FM) model, which is a promising candidate to describe the anomalous diffusion in brain tissues [24]. An anisotropy metric was introduced and applied to the FM-related parameters, including the Noah exponent (α) and the Hurst exponent (H) [36]. A receiver operating characteristic (ROC) analysis was performed to evaluate the performances of the anisotropy metric values, as well as their combinations with the commonly used directionally averaged values, for tumor differentiation.

2. Material and methods

2.1. 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 prior to the treatment of tumors; (b) the patient had no concurrent brain diseases unrelated to the tumor; and (c) a histopathological diagnosis of glioma was assigned after surgical resection.

Twenty-two patients were eligible and thus 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 [37], 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.

2.2. Image acquisition

MR imaging was performed on a 3 T GE Discovery MR750 MRI scanner (GE Healthcare, Milwaukee, Wisconsin) equipped with an 8-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 arrayed at 27.5, 40.0, and 55.5 ms. For each Δ value, the diffusion gradient amplitude (G_0) was arrayed 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 (δ) was kept constant at 20.4 ms. Therefore, a total of 18 non-zero 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/mm^2). The diffusion gradients were successively applied along the x-, y-, and z-axes. In addition, a total of 12 images without diffusion sensitization ($b = 0$) were obtained. The other data acquisition parameters for this diffusion sequence were as follows: 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 T_1-weighted imaging and T_2-weighted imaging.

2.3. Image analysis

Prior to image analysis, the acquired images were corrected for eddy current distortions and head motion using FSL tools [38]. ADC maps were calculated using the images acquired at b-values of 0 and 954 s/mm^2, which is the closest to the conventional 1000 s/mm^2 b-value in the dMRI acquisition. The images were analyzed using the FM model. According to the FM-based dMRI theory [24], the diffusion-induced signal decay can be formulated as.

$$S/S_0 = \exp(-\eta D_{\alpha,H} \gamma^{\alpha} G_0^{\alpha} \Delta^{\alpha+\alpha H}) \tag{1}$$

where $D_{\alpha,H}$ is the generalized diffusion coefficient of anomalous diffusion, and γ is the gyromagnetic ratio. As mentioned above, G_0 is the diffusion gradient amplitude, and Δ is the gradient separation time. In Eq. (1), η is a dimensionless number, which can be determined with α, H, δ, and Δ in the following form:

$$\eta = \frac{1}{(1+\mu)^{\alpha}} \left[\int_0^{\delta/\Delta} \left| \left(\frac{\delta}{\Delta} + 1 - u\right)^{1+\mu} - (1-u)^{1+\mu} - \left(\frac{\delta}{\Delta} - u\right)^{1+\mu} \right|^{\alpha} du + \int_{\delta/\Delta}^{1} \left| \left(\frac{\delta}{\Delta} + 1 - u\right)^{1+\mu} - (1-u)^{1+\mu} \right|^{\alpha} du + \int_1^{1+\delta/\Delta} \left(\frac{\delta}{\Delta} + 1 - u\right)^{\alpha+\alpha\mu} du \right] \tag{2}$$

where $\mu = H - 1/\alpha$. The signal attenuation at each voxel was fitted to Eq. (1) separately along each direction. The fitting procedures were performed using the trust-region-reflective nonlinear fitting algorithm in MATLAB (MathWorks, Natick, MA).

To quantify anisotropy, a metric similar to FA, termed generalized FA (gFA), was introduced as the sample standard deviation dividing the root mean square [35]:

$$gFA(V) = \sqrt{\frac{N}{N-1} \frac{\sum_{i=1}^{N} (V_i - \overline{V})^2}{\sum_{i=1}^{N} V_i^2}} \tag{3}$$

where N is the number of sampling directions, which equals 3 in this study, and V represents the parameter to be measured. V_i is the value in the i-th direction, and $\overline{V}$ is the directionally averaged value. The gFA maps were calculated for ADC, α, and H.

Two radiologists (Z.W., L.S.) who were in consensus manually drew the region of interest (ROI) for tumor and normal-appearing white