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Differentiating Low- and High-Grade Pediatric Brain Tumors Using a Continuous-Time Random-Walk Diffusion Model at High *b*-Values

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Abstract

Purpose—To demonstrate that a recently proposed continuous-time-random walk (CTRW) diffusion model can be adapted to human brain imaging, and to illustrate that the CTRW model can improve the diagnostic accuracy of differentiating low-grade and high-grade pediatric brain tumors.

Theory and Methods—Fifty-four children with histopathologically confirmed brain tumors (24 low-grade, 30 high-grade) underwent MRI scans at 3T. Diffusion-weighted images, acquired with 12 *b*-values (0 to 4000 s/mm²), were fit to a simplified CTRW diffusion model to extract three parameters: anomalous diffusion coefficient, D_m , and temporal and spatial heterogeneity parameters, α and β , respectively. The two latter parameters have been linked to intra-voxel tissue heterogeneity. With histopathology results as a reference, a *k*-means clustering algorithm and a receiver operating characteristic (ROC) analysis were employed to determine the sensitivity, specificity, and diagnostic accuracy of using the CTRW parameters for differentiating the tumor grades.

Results—The CTRW diffusion model was successfully applied to data obtained from the living human brain using a 3T MRI scanner with clinically achievable *b*-values up to 4000 s/mm². Significant differences between the two tumor groups were observed in all three individual CTRW parameters with *p*-values < 0.001. The *k*-means analysis showed that the combination of the three CTRW parameters produced higher diagnostic accuracy (85% vs. 75%) and specificity (83% vs. 54%) than the apparent diffusion coefficient (ADC) from a mono-exponential model in differentiating the grades of pediatric brain tumors. In addition, the ROC analysis revealed that any

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combination of the CTRW parameters gave a larger area under the curve (0.90–0.96) than using ADC alone (0.80).

Conclusion—With its sensitivity to intra-voxel heterogeneity, the simplified CTRW diffusion model has provided a set of new parameters that are useful for non-invasive brain tumor grading for pediatric patients. The proposed technique is particularly valuable in situations where surgical biopsy is not feasible due to the tumor location.

Keywords

Pediatric brain tumor; non-Gaussian diffusion; continuous-time-random-walk; tumor grading; high *b*-value diffusion imaging

Introduction

Pediatric brain tumors are the second most common childhood cancer, accounting for ~23% of all pediatric cancers in the U.S.¹ Over the past few decades, a number of treatment strategies have been developed to manage this disease, including surgical resection, chemotherapy, radiotherapy, targeted therapy, and surveillance². The choice of these treatment options depends on the age of the child, location of the lesion, and, in particular, the tumor type and grade. The low-grade (grades I and II) tumors are typically less aggressive, justifying more conservative treatments. In contrast, high-grade (grades III and IV) tumors are more malignant and require aggressive treatment such as total surgical resection, followed by chemotherapy and/or radiation. Therefore, differentiation between low and high grade is one of the most important aspects in managing childhood brain tumors.

Image-guided stereotactic biopsy, followed by histopathology analysis, is the standard approach to determine tumor type and grade. However, this approach cannot be applied to all pediatric brain tumors. For example, for tumors located at the brain stem, a common site for pediatric brain tumors, biopsy can be prohibitive because of the significant risks associated with the invasive procedure^{3,4}. Even for tumors where biopsy is feasible, sampling errors can compromise the diagnostic accuracy despite the use of the most advanced stereotactic system⁵. Noninvasive diagnostic imaging of the tumor is thus needed to overcome these limitations.

Conventional MRI, including T1-weighted (T1W), T2-weighted (T2W), and T2 fluid attenuated inversion recovery (FLAIR) sequences, has been employed for differentiating low- and high-grade brain tumors. The overlapping signal characteristics, however, make the differentiation challenging and sometimes unreliable⁶, particularly for pediatric brain tumors⁷. For instance, pilocytic astrocytomas, a common type of low-grade pediatric brain tumors, show significant contrast enhancement which is typically observed in high-grade brain tumors. Advanced MR techniques, such as MR spectroscopy, perfusion imaging, and diffusion imaging, can improve tumor grading by characterizing changes in brain metabolism, relative cerebral blood volume (rCBV), volume transfer coefficient (k_{trans}), apparent diffusion coefficient (ADC), and other parameters. Among these techniques, quantitative diffusion imaging using ADC has attracted immense attention because of its

simplicity, fast imaging time, and the possible relationship between ADC and tissue cellularity^{8–10}. Despite the potential, published studies based on ADC measurements indicate that there remains a significant overlap between low- and high-grade brain tumors^{11–14}.

ADC is derived from a mono-exponential diffusion model, $\exp[-bD]$ (D : diffusion coefficient, b : the b -factor), which assumes Gaussian diffusion where the diffusion medium is typically homogeneous. Given the heterogeneous nature of biological tissues, particularly the brain tumors that exhibit a high degree of structural heterogeneity (neoplastic cells, edema, necrosis, hemorrhage, etc.) and complexity (cellularity, angiogenesis, etc.), it is well known that water diffusion in tissues does not follow a Gaussian distribution. Over the past decades, a number of non-Gaussian diffusion models, such as bi-exponential¹⁵, stretched-exponential¹⁶, statistical¹⁷, q -space¹⁸, kurtosis¹⁹, and fractional-order calculus (FROC)^{20,21} models, neurite orientation dispersion and density imaging (NODDI)²², composite hindered and restricted model of diffusion (CHARMED)²³, anomalous diffusion model in random disordered media and fractal spaces²⁴, and many others^{25–27}, have been developed with a common goal to reveal the underlying tissue structures and environment by measuring the anomalous, non-Gaussian diffusion behavior. Some of these models have been used successfully to improve differentiation of low- and high-grade adult and pediatric brain tumors^{13,28–31}.

Most recently, an extension of the FROC diffusion model based on the continuous-time random-walk (CTRW) theory was introduced³². Unlike other non-Gaussian diffusion models, the CTRW diffusion model recognizes intra-voxel diffusion heterogeneity in both time (i.e., water molecules can take a variable amount of time to make a move, which we call ‘water trapping’) and space (i.e., water molecules can diffuse with drastically different free length, which we call ‘water jumping’). These diffusion heterogeneities can directly reflect intra-voxel structural heterogeneity, which is related to tissue complexity and micro-environment. The probabilistic nature of the CTRW theory relaxes *a priori* distributions of waiting times and distance increments of water molecular diffusion, providing a more realistic description of the complex structures of biological tissues. In a previous study, this model was demonstrated on fixed rat brain using microscopic MRI scanning at 17.6 T with a strong gradient (525 mT/m), which features high signal-to-noise ratio (SNR) and high b -values (e.g., up to 25,000 s/mm²) with a relatively short echo time (e.g., TE = 28 ms). The goal of this study is to extend the application of the CTRW model to living human subjects at a clinical magnetic field strength of 3 Tesla with a commonly available gradient (e.g., 40 mT/m) and echo time (e.g. TE = 100 ms). Furthermore, we aim to demonstrate that a new set of parameters from the CTRW model can be used to improve the diagnostic accuracy of differentiating low- and high-grade pediatric brain tumors.

Theory

The simple random-walk diffusion model yields a Gaussian distribution of the displacement whose mean square is proportional to diffusion time. When the random-walk model is generalized to the CTRW model in both time and space to account for the complexity and heterogeneity of the diffusion environment in tissues, the jump distance and jump waiting

time of water molecules are no longer constrained by a Gaussian distribution. In this generalized case, the mean-square displacement (MSD), $\langle x^2(t) \rangle$, can be represented by a power law, $\langle x^2(t) \rangle \sim t^{\alpha/\beta'} \equiv t^\gamma$, where t is the diffusion time, and α and β' are the fractional powers on the waiting time and jump length probability distributions, respectively^{21,33}. When $\alpha = 1$ and $\beta' = 2$ (i.e. $\gamma = 1$), this formalism is reduced to the MSD in Gaussian diffusion (i.e., normal diffusion). In contrast, when $\gamma > 1$ or $\gamma < 1$, the anomalous diffusion process is referred to as super-diffusion or sub-diffusion, respectively, which is already known in hydromechanics³⁴.

In the context of the CTRW theory, the content $S(x, t)$ of water molecules (which is proportional to the measured magnetization) in a heterogeneous tissue is described with a dual space-time fractional order diffusion equation

$${}_0^C D_t^\alpha (S(x, t)) = D_{\alpha, \beta'} \frac{\partial^{\beta'} S(x, t)}{\partial |x|^{\beta'}}, \quad (1)$$

where ${}_0^C D_t^\alpha$ is the α^{th} fractional order time derivative in Caputo form³⁵, $\partial^{\beta'} / \partial |x|^{\beta'}$ is the β'^{th} fractional order space derivative in the Riesz form³⁶, and $D_{\alpha, \beta'}$ is the generalized diffusion coefficient (in $\mu\text{m}^{\beta'}/\text{s}^\alpha$). In the continuum limit, the solution of the generalized diffusion formulism in Eq. (1) yields a characteristic decay process that is represented by a Mittag-Leffler function (MLF)³²,

$$E_\alpha(z) = \sum_{k=0}^{\infty} \frac{z^k}{\Gamma(\alpha k + 1)}. \quad (2)$$

By defining $\beta = \beta'/2$, $b = q^2(-\delta/3)$, and $\bar{b} = (-\delta/3)$, where δ and $\bar{b}$ are the Stejskal-Tanner diffusion gradient pulse width and gradient lobe separation, respectively, and q is the q -space variable, the solution to Eq. (1) in the context of a Stejskal-Tanner diffusion gradient can be described as

$$M(q) = M_0 E_\alpha \left(-D_{1,2} \frac{\tau^{1-\alpha}}{\mu^{2-2\beta}} |q|^{2\beta} \bar{\Delta}^\alpha \right), \quad (3)$$

where M is the measured magnetization whose initial equilibrium value is M_0 . In Eq. (3), E_α is a MLF, $D_{1,2}$ is the nominal diffusion coefficient (in mm^2/s), μ (in μm) and τ (in ms) are spatial and temporal parameters, respectively, that are needed to preserve the nominal units of diffusion coefficient. By substituting q^2 with $b/\bar{b}$, Eq. (2) can be written as

$$M(b)=M_0 E_{\alpha} \left(-D_{1,2} \frac{\tau^{1-\alpha}}{\mu^{2-2\beta}} b^{\beta} \bar{\Delta}^{(\alpha-\beta)} \right). \quad (4)$$

In order to reduce the computational complexity of estimating the model parameters, the solution in Eq. (4) can be simplified by defining the β^{th} power of the an “anomalous diffusion coefficient” D_m as

$$D_m^{\beta} \equiv D_{1,2} \frac{\tau^{1-\alpha}}{\mu^{2-2\beta}} \bar{\Delta}^{(\alpha-\beta)}. \quad (5)$$

The magnetization in Eq. (4) can then be written in the form of the MLF as

$$M(b)=M_0 E_{\alpha}(-(bD_m)^{\beta}), \quad (6)$$

where D_m which we call “anomalous diffusion coefficient” thereafter, is in units of $\mu\text{m}^2/\text{s}$.

Equation (6) provides a simplified mathematical expression from which the anomalous diffusion coefficient, D_m and the two parameters (α and β) related to diffusion heterogeneity in time and space, respectively, can be estimated by using the multi- b -value diffusion imaging data via a nonlinear fitting. With this simplification, D_m can be compared directly to ADC obtained from a mono-exponential model. Importantly, the temporal and spatial diffusion heterogeneities reflected by α and β , respectively, offer a means to quantify the heterogeneous nature of the intra-voxel tissue structure and environment.

Methods

Patient Characteristics

The CTRW diffusion model was employed for differentiating low- and high-grade pediatric brain tumors. Under approval by the institutional review board and with written informed consents of the legal guardians of all participating subjects, this prospective study involved 54 children (16 females from 4 months to 9 years old and 38 males from 4 months to 13 years old) with histopathologically proven brain tumors. According to the 2007 World Health Organization (WHO) classification³⁷, histopathology showed that 24 patients had low-grade (WHO grade I or II) tumors, consisting of 9 pilocytic astrocytoma, 8 astrocytic astrocytoma, 2 ependymoma, 3 dysembryoplastic neuro epithelial tumors (DNET), and 2 choroid plexus papilloma. The remaining 30 patients were diagnosed with high-grade (WHO grade III or IV) tumors, including 11 medulloblastoma, 4 teratoid/rhabdoid tumor (AT/RT), 2 glioblastoma multiforme (GBM), 3 germinoma, 2 pineoblastoma, 2 anaplastic ependymoma, 2 ependymoblastoma, 2 primitive neuroectodermal tumor (PNET), 1 anaplastic astrocytoma, and 1 malignant teratoma. This study did not focus on analyzing the differences among the tumor subtypes because of the limited number of patients.

Image Acquisition

All patients underwent MRI examination on a 3 Tesla scanner (Signa HDxt, GE Health Care, Milwaukee, WI, USA) with an 8-channel phased-array head coil (Invivo Corp., Gainesville, FL). The MRI examination included pre- and post-contrast T1W imaging with FLAIR (TR/TE = 2200/22 ms, flip angle = 90°, TI = 860 ms, matrix size = 320×224, FOV = 22 cm × 22 cm, slice thickness = 5 mm), T2W imaging with fast spin echo (TR/TE = 3000/117 ms, echo train length = 24, matrix size = 320×224, FOV = 22 cm × 22 cm, slice thickness = 5 mm), T2 FLAIR (TR/TE = 8000/120 ms, TI = 2250 ms, echo train length = 24, matrix size = 320×224, slice thickness = 5 mm, FOV = 22 cm × 22 cm), and high b -value diffusion-weighted (DW) imaging for the CTRW model analysis. The DW images were acquired using a single-shot spin-echo echo planar imaging (EPI) sequence with 12 b -values (0, 10, 20, 50, 100, 200, 400, 800, 1200, 2000, 3000, and 4000 s/mm²). At each non-zero b -value, trace-weighted images were obtained by applying a Stejskal-Tanner diffusion gradient along the x , y , and z directions successively to minimize the effect of diffusion anisotropy. The other data acquisition parameters for the diffusion sequence were: TR/TE = 4700/100 ms, acceleration factor = 2, separation between the Stejskal-Tanner gradient lobes () = 38.6 ms, duration of each diffusion gradient (δ) = 32.2 ms, FOV = 22 cm × 22 cm, matrix size = 128×128 (zero-padded to 256×256), and slice thickness = 5 mm. The TR value was selected to keep the total scan time to be ~ 3 minutes to facilitate clinical use. The relatively short TR may cause signal saturation. However, its impact on Eq. (6) is minimal since the saturation affects M_0 and $M(b)$ equally.

CTRW Modeling

The parameters (D_m , α , and β) of the CTRW model were estimated by fitting Eq. (6) to the acquired multi- b -value diffusion images on a voxel-by-voxel basis. An iterative Levenberg-Marquardt method in the Matlab Optimization Toolbox (MathWorks, Inc., Natick, MA) was employed for the non-linear least squares fitting. To filter out the pixels with low SNR, a noise threshold was set at $n+2\sigma$, where n and σ are the mean and standard deviation of the noise in the background, respectively²¹. Pixels with intensity below the threshold were not included in the calculation. The diffusion images, M_{raw} , were also corrected for Rician noise

using $M_{rc} = \sqrt{M_{raw}^2 - 2\sigma_n^2}$, where M_{rc} is the Rician noise corrected signal and σ_n is standard deviation of the real or imaginary components of the noise. The noise bias, $2\sigma_n^2$, can be calculated as the average value of the magnitude squared signal of the background³⁸. After the noise rejection and Rician noise correction, the nonlinear fitting proceeded with two major steps: (a) estimating D_m by a mono-exponential model using the diffusion images at low b -values ($b \leq 1200$ s/mm²), and (b) simultaneously estimating α and β from all images (b -values = 0 – 4000 s/mm²) after fixing each voxel's D_m at its estimated value. This approach resulted in an anomalous diffusion coefficient, D_m , that can be directly compared to the ADC value obtained from a mono-exponential diffusion model.

Statistical Analysis

After the maps of D_m , α , and β were produced, a statistical analysis was performed on the voxel-wise estimates of D_m , α , and β in the tumor regions of interest (ROIs) of each patient. The selection of the tumor ROIs was performed in each tumor-containing slice by including

only the solid region of the tumor. The mean values of the estimated D_m , α , and β were then computed over the tumor ROIs from the combination of all tumor-containing slices. This was followed by combining the CTRW model parameters from all patients in each group prior to performing a non-parametric Mann-Whitney-Wilcoxon U-test with a significance set at $p < 0.05$ for evaluating each individual CTRW parameter between the low- and high-grade tumor groups.

Unlike the conventional mono-exponential model that produces a single diffusion coefficient, the CTRW model provides three diffusion parameters, allowing the use of multivariate analysis methods. To utilize this feature, two approaches were evaluated for differentiating low- and high-grade brain tumors. Firstly, a k -means algorithm was employed by optimizing the total intra-cluster variance in the absence of prior histopathological information³⁹. For our study, the dataset with the mean CTRW parameter values had $n = 54$ elements (i.e., the number of the patients) and $k = 2$ clusters (i.e., low- and high-grade tumors). To investigate the contribution of CTRW parameters to such differentiation, k -means clustering analyses were performed with a two-dimensional clustering by using the mean estimate pairs of (D_m, α) , (D_m, β) , and (α, β) , respectively; and a three-dimensional clustering by using the three mean estimates (D_m, α, β) jointly. With each combination, the sensitivity, specificity, and diagnostic accuracy were computed by comparing the results of the cluster analysis against the known histopathological findings. Secondly, the receiver operating characteristic (ROC) curves were constructed by performing a multivariate logistic regression analysis⁴⁰ for different combinations of the CTRW parameters: (D_m, α) , (D_m, β) , (α, β) , and (D_m, α, β) . The test variables used to create the ROC curves were composed of the probabilities from the logistic regression model, whereas the state variable was considered to be the 'true' tumor category obtained from the histopathological information. The performance of using the CTRW parameters for differentiating between the low- and high-grade pediatric brain tumors was assessed by sensitivity, specificity, diagnostic accuracy, and area under the curve (AUC). Both the k -means and ROC analyses were carried out in Matlab (MathWorks, Inc., Natick, MA).

Results

The CTRW diffusion model was successfully applied to data acquired from the living human brain using a 3T clinical scanner equipped with a maximal gradient of 40 mT/m. Representative imaging results from the low- and high-grade patient groups are given in Fig. 1 (WHO grade II ependymoma, 17 month-old boy) and Fig. 2 (WHO grade IV medulloblastoma, 18 month-old boy), respectively. Each panel of axial images contains the pre-contrast T1W FLAIR (a), post-contrast T1W FLAIR (b), T2W EPI (c), and color-coded maps of D_m , α , and β (d-f). The pre-contrast T1W and T2W images, as well as post-contrast T1W images obtained from both patients (Figs. 1a–1c and Figs. 2a–2c) showed similar contrast enhancement and other signal characteristics, making the differential diagnosis difficult. In contrast, all of the CTRW parameters in the high-grade tumor (D_m : 0.56 $\mu\text{m}^2/\text{ms}$, α : 0.88, β : 0.80 in Fig. 1) were substantially lower than those in the low-grade tumor (D_m : 1.1 $\mu\text{m}^2/\text{ms}$, α : 0.97, β : 0.95 in Fig. 2), with changes ranging from 10–65%. The same trend was preserved when combining all patient data in each group, as summarized in Table 1 where mean D_m , α , and β parameters in high-grade tumor group were lower by

66%, 4%, and 13%, respectively, as compared with the low-grade group. Figure 3 displays the boxplots of the mean D_m , α , and β values of all the low- and high-grade tumors, further demonstrating the separation between the two groups with significantly lower CTRW parameter values in the high-grade than in the low-grade tumors (p -values < 0.001). The results given in Fig. 3 and Table 1 along with the comparison of Figs. 1 and 2 imply that the CTRW parameters can be used as a quantitative biomarker to differentiate the two tumor groups.

Figure 4 shows the performance of using the k -means algorithm to differentiate between the low- and high-grade tumors in the three-dimensional scatter plots with each of the three CTRW parameters (D_m , α , β) representing an axis. Figure 4a illustrates the distribution of the low- (red) and high-grade tumors (blue) according to the histopathology results (true classification), while Fig. 4b shows the same data but using the k -means algorithm for classification based solely on the CTRW parameters. Qualitatively, the close resemblance of the CTRW-based classification to the “true classification” indicates good performance of the CTRW parameters for differentiating the tumor grades. The performance of the k -means clustering based on all four combinations of the CTRW parameters [i.e., (D_m , α), (D_m , β), (α , β), and (D_m , α , β)] was quantitatively evaluated using sensitivity, specificity, and diagnostic accuracy, as summarized in Table 2. Among the different combinations of the CTRW parameters, (α , β) or (D_m , α , β) gave the best accuracy (85%) with a sensitivity of 86% and a specificity of 83%. For comparison, the k -means algorithm was also applied to the ADC values for separating the two tumor groups (last column in Table 2). Although ADC values provided a high sensitivity (93%), the specificity was rather poor (54%), which led to the sub-optimal accuracy (75%). The specificity was considerably improved using any combinations of the CTRW parameters, particularly the combination of (D_m , α) (Table 2).

The performance of the CTRW parameters is further illustrated in the ROC analysis for differentiating low-grade (negative) and high-grade (positive) pediatric brain tumors. The results of the ROC analysis are given in Fig. 5 in which the ROC curves for the combined CTRW parameters (D_m , α), (D_m , β), (α , β), and (D_m , α , β), and for the ADC value are displayed. The best cut-off sensitivity and specificity values that could be reached for each ROC curve are indicated by an open circle. As shown in Fig. 5 and summarized on Table 3, the combination of D_m , α , and β yielded the largest area under the ROC curve (AUC = 0.958) and the highest specificity cut-off value (0.916). Importantly, the combinations of the CTRW parameters provided similar sensitivity to ADC (~93%), but considerably higher specificity (~91% vs. 70%) and AUC (~0.95 vs. 0.80) than using ADC for differentiation of low- and high-grade pediatric brain tumors.

Discussion

In this study, we have demonstrated the feasibility to differentiate low- from high-grade pediatric brain tumors using a set of new parameters (D_m , α , and β) obtained from a CTRW diffusion model. Our results have shown significant differences ($p < 0.001$) in the CTRW parameters either individually or jointly, between the two tumor groups. The high-grade tumors exhibited considerably lower values of D_m , α , and β compared with the low-grade ones. Using a k -means clustering analysis, we have further demonstrated that combinations

of the CTRW parameters can improve the specificity (83% vs. 54%) and accuracy (85% vs. 75%) for differentiating low- and high-grade groups compared to the approach relying on ADC values. This result was further confirmed using an independent ROC analysis, which showed that the combination of all CTRW parameters improved the predictive quality with a larger AUC (0.957) than the ADC alone (AUC = 0.804). Although the exact mechanisms behind the substantial changes in the CTRW parameters are not clear, our experimental observations can be significant as they show the feasibility of a non-invasive imaging approach for differentiating low- and high-grade pediatric brain tumors with a high diagnostic accuracy (0.85). This is particularly important for pediatric brain tumors at or near the brain stem where tissue biopsy is difficult, risky, or prohibitive.

ADC values have been widely used to assess cellularity and tissue micro-structures in tumors to improve diagnosis or to monitor treatment response^{8,41–43}. Despite its success in many applications, overlap in ADC values has been a primary limitation for differentiating low- and high-grade brain tumors, which leads to suboptimal specificity and diagnostic accuracy as reported by others^{10–14,41} and observed in this study. One important distinction between the low- and high-grade tumors lies in tissue heterogeneity. High-grade brain tumors are hallmarked by an increased degree of tissue heterogeneity due to the presence of hemorrhage, necrosis, vasogenic edema, and rich capillaries together with neoplastic cells^{30,37,44}. In contrast, intra-tumor heterogeneity is less developed in low-grade tumors compared to their high-grade counterparts⁴⁵. In DW imaging, where the typical voxel size is as large as $2 \times 2 \times 3 \text{ mm}^3$, the intra-tumor heterogeneity can be reflected at the voxel level as multiple tissue structures (intra-cellular space, extra-cellular space, capillaries, etc.) and types (necrosis, edema, calcification, hemorrhage, etc.), which can co-exist in a voxel. This intra-voxel ‘structural heterogeneity’ provides an environment that leads to a heterogeneous diffusion process within a voxel. Unfortunately, a single ADC value from the mono-exponential model averages out the heterogeneous nature of the diffusion process and disguises the rich information on intra-voxel structural heterogeneity that can be valuable for characterizing tumors.

Unlike the mono-exponential model, the CTRW model incorporates intra-voxel diffusion heterogeneity into the classical Fick’s equation by using two fractional order parameters, α and β , with respect to time and space, respectively. The β parameter, initially introduced in a predecessor model (a.k.a, the FROC model) to the CTRW model, was intended to account for the non-Gaussian distribution of diffusion displacement^{20,21,46} and has been related to the heterogeneous diffusion jump length³² associated with intravoxel spatial heterogeneity. The β parameter is mathematically equivalent to the heterogeneity index empirically introduced by Bennett et al.¹⁶ in the stretched-exponential model, and has been found to be closely related to tissue heterogeneity in a number of studies^{30,47,48}. Unlike the empirical stretched-exponential approach, the CTRW model has mathematically linked β to non-Gaussian diffusion behavior by considering the anomalous water diffusion jump length in super- or sub-diffusion processes. In addition, it should be noted that the CTRW and stretched-exponential models are equivalent at low b -values²⁰.

The temporal parameter, α (dimensionless), is specific to the CTRW model and has not been introduced in other models. It reflects the temporal heterogeneity of the diffusion process,

that is, the likelihood of the water molecule to be “trapped” or “released” while it diffuses through the complex tissue structure and environment. Although the spatial heterogeneity (represented by β) and the temporal heterogeneity (represented by α) both originate from the underlying tissue structural heterogeneity, they reflect two independent and complementary aspects of diffusion heterogeneities; water molecules can take a variable time to make a move, or can produce a variable displacement in each move. In this study, both α and β showed measurable differences between the low- and high-grade pediatric brain tumors, although β exhibited a greater sensitivity (Table 1).

In addition to the two parameters related to the different aspects of diffusion heterogeneity, the CTRW model also yields an anomalous diffusion coefficient D_m . The mathematical simplification presented in the Theory section gives a D_m with the same units as the conventional ADC, allowing for a direct comparison. In this study, additional effort was also made towards equalizing D_m with ADC by performing the fitting using only the low b -value images to estimate D_m . The sensitivity, diagnostic accuracy, and AUC that were obtained by using D_m alone (0.96, 0.77, and 0.952, respectively) have been found to be higher than those obtained from ADC (0.93, 0.75, and 0.804, respectively), whereas both parameters yielded the same specificity (0.54). The close resemblance between D_m and ADC enables the CTRW model be used without losing the traditional diffusion coefficient which can be useful in specific applications such as improving the sensitivity of tumor differentiation (Table 3) or detecting ischemic lesions⁴⁹. A number of recent studies have investigated the relationship between β and tissue heterogeneity. In a recent study by Kwee et al., high-grade adult gliomas were characterized by using a stretched-exponential model through a comparison with normal brain structures³⁰. The empirical heterogeneity index, which is equivalent to β in our study, was found to be significantly lower in high-grade tumors than the unaffected brain tissue as a result of increased cellularity, vascular density, and protein content which lead to more restricted diffusion. In a more recent study³¹, the β parameter was investigated using the FROC model (i.e., assuming the fractional time derivative $\alpha = 1$) for improving differentiation between low- and high-grade pediatric brain tumors. The present study expanded the scope of tumor characterization by recognizing intra-voxel diffusion heterogeneity in both time and space. It is important to note that when all three parameters are combined, α noticeably contributed to the improvement in both sensitivity and diagnostic accuracy (Table 2). The ability of combining multiple parameters is a significant advantage of the CTRW diffusion model compared to the widely used mono-exponential diffusion model as well as the more sophisticated stretch exponential and FROC models.

This study has several limitations. First, although our results suggest a possible relationship between the CTRW parameters and tissue heterogeneity, a direct correlation between the CTRW parameters and tissue structure is lacking. This is partially because no image-guided biopsy/surgery was attempted in this study. Even with image-guided biopsy/surgery, such a correlation would still be difficult because of the elastic nature of brain tissues leading to sampling inaccuracy⁵. Although the difference of the CTRW parameters between the two tumor groups is significant, we have not been able to pinpoint the histological basis (e.g., cell size distribution, cytoplasm ratio, extents of necrosis, etc.) of the change in each individual parameter. Such a correlation may be established through an *in vitro* study

involving postmortem samples. Second, the intra-voxel heterogeneity inferred from the CTRW parameters is expected to be dependent on the voxel size. As the voxel size changes, the degree of intra-voxel tissue heterogeneity seen by the CTRW parameters is likely to change. This important aspect remains to be explored. Third, the α parameter is expected to be dependent on the diffusion time, Δ , and the diffusion gradient pulse width, δ . Constrained by the echo time in order to preserve the SNR, this important aspect was not explored in the present study. With the availability of strong gradient on a human scanner⁵⁰, investigating the impact of the diffusion time on the CTRW parameters is expected to provide new insights into the tissue structure and the associated heterogeneity. Fourth, constrained by the total acquisition time, the present study did not explore the anisotropic aspect of the diffusion process and the possible tensor or vector descriptions of the CTRW parameters. Instead, the possible anisotropic effect was suppressed by performing the analysis using the trace-weighted diffusion images. Finally, the study is limited to a specific application on pediatric brain tumors. As a new technique sensitive to intra-voxel tissue heterogeneity, the CTRW model is expected to have a much broader application for characterizing healthy and pathologic tissues and monitoring progression and regression of a number of disease processes.

Conclusion

We have shown that the CTRW model can be successfully applied to *in vivo* human studies on a clinical 3 Tesla MRI scanner. More importantly, we have demonstrated that the CTRW model provides a set of novel diffusion parameters that can improve differentiation of low- from high-grade pediatric brain tumors with relatively high specificity (0.83), diagnostic accuracy (0.85), and predictive quality (AUC = 0.957). The added value afforded by the CTRW model, in combination with the conventional ADC measurement, represents an important development towards non-invasive, imaging-based brain tumor grading for pediatric patients, particularly in situations where surgical biopsy is not feasible.

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Fig 1.

An example of a low-grade brain tumor from a 17 months old boy (ependymoma, WHO grade II). *Top row:* axial pre-contrast T1W FLAIR (a), post- contrast T1W FLAIR (b), and T2W EPI (c) images. *Bottom row:* maps of the CTRW parameters, D_m , α , and β (d-f, respectively). The solid tumor ROI, which was initially drawn on the T2W EPI image with the aid of T1W images, is shown with black contours in d-f. The enhancement is seen in (b). The values D_m , α , and β within the ROI are higher than those in Fig. 2 for a high-grade brain tumor.

Fig 2.

An example of a high-grade brain tumor from an 18 months old boy (medulloblastoma, WHO grade IV). *Top row:* axial pre-contrast T1W FLAIR (a), post- contrast T1W FLAIR (b), and T2W EPI (c) images. *Bottom row:* maps of the CTRW parameters, D_m , α , and β (d–f, respectively). The solid tumor ROI, which was initially drawn on the T2W EPI image with the aid of T1W images, is shown with black contours in d-f. Although the signal characteristics (including contract enhancement) of top-row images (a–c) are similar to those of the low-grade tumor in Fig. 1 (a–c), the values D_m , α , and β within the ROI (d–f) are significantly lower than those in Fig. 1 (d–f).

Fig 3.

Box and whisker plots of mean values of the CTRW parameters, D_m (a), α (b), and β (c), for low- and high-grade pediatric brain tumors. The central boxes represent the values from the lower to upper quartile whereas the middle line represents the median. The red “+” symbol denotes the outliers that are more than 1.5 times the interquartile range from the quartiles. The CTRW parameters exhibited a statistically significant difference between the low- and high-grade pediatric brain tumor groups with p -values < 0.001 .

Fig 4.

Three-dimensional scatter plots of the mean CTRW parameters, (D_m, α, β) , with colorization based on histopathology (a), and based on k -means clustering analysis results (b). Each dot represents a low-grade (in red) or high-grade patient (in blue).

Fig 5. ROC curves of using the combinations of D_m , α , and β , and the conventional ADC value for differentiating between low-grade and high-grade pediatric brain tumors. The empty circles are the best cut-off sensitivity and specificity values that could be reached for each ROC curve. The AUCs for the corresponding ROC curves are 0.951 (D_m and α), 0.952 (D_m and β), 0.898 (α and β), 0.957 (D_m , α , and β), and 0.804 (ADC).

Table 1

The descriptive statistics, sample mean and standard deviation, ($\bar{x} \pm \sigma$) of the CTRW model parameter values for low- and high-grade tumor groups.

	D_m (in $\mu\text{m}^2/\text{ms}$)	α	β
Low-grade ($n = 24$)	1.5 $\pm$ 0.5	0.941 $\pm$ 0.039	0.930 $\pm$ 0.071
High-grade ($n = 30$)	0.75 $\pm$ 0.2	0.900 $\pm$ 0.036	0.813 $\pm$ 0.072
<i>p</i>-value	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$

Table 2

Sensitivity, specificity, and accuracy of the k -means clustering analysis implemented on the CTRW parameters for tumor differentiation. The results from ADC analysis are listed in the last column for comparison.

	(D_m, α)	(D_m, β)	(α, β)	(D_m, α, β)	ADC
Sensitivity	0.60	0.70	0.86	0.86	0.93
Specificity	0.91	0.83	0.83	0.83	0.54
Accuracy	0.74	0.75	0.85	0.85	0.75

Table 3

Sensitivity and specificity cut-off values and the AUC of the ROC analysis for the different combinations of the CTRW parameters and the ADC values for tumor differentiation.

	(D_m, α)	(D_m, β)	(α, β)	(D_m, α, β)	ADC
Specificity cut-off	0.875	0.916	0.833	0.916	0.708
Sensitivity cut-off	0.900	0.933	0.933	0.933	0.933
AUC	0.951	0.952	0.898	0.957	0.804