Differentiation of Low- and High-Grade Pediatric Brain Tumors Using A Non-Gaussian Diffusion Model

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Introduction

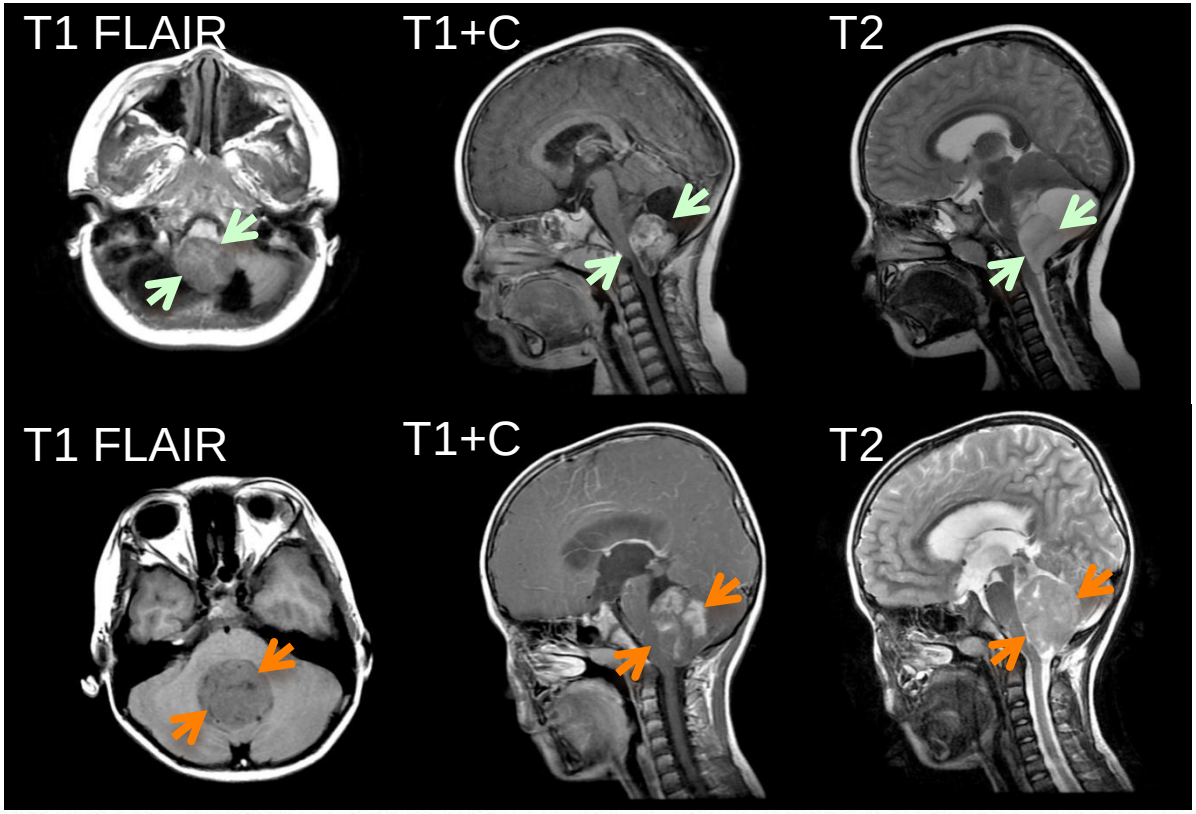
- Pediatric brain tumors are the most common solid tumors in children.
- Differentiation between low-grade and high-grade brain tumors has prognostic significance.
- Brain biopsy may not be an option due to the inoperable location in the areas such as brain stem.
- The noninvasive diagnosis is not only desirable but also required.

Introduction

- Accurate differentiation of low-grade and high-grade brain tumors using MRI is challenging.
- Conventional T1w / T2w imaging has limited specificity.

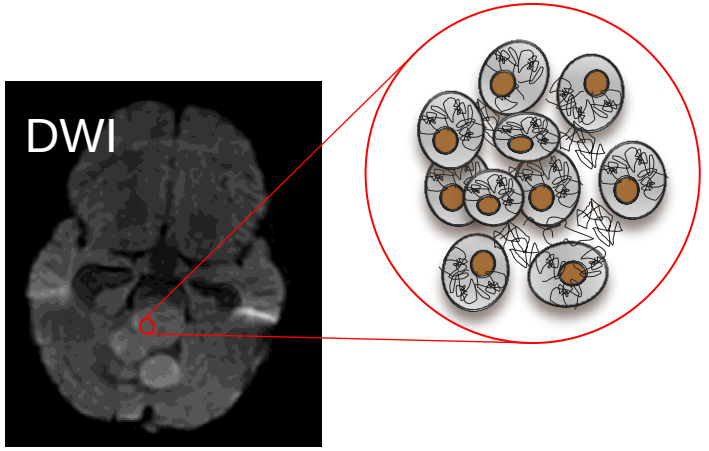
Low-grade
Pilocytic Astrocytoma

High-grade
Medulloblastoma



Diffusion MR Imaging for Brain Tumors

- Diffusion MR Imaging is able to reveal the cellular information of brain tissues*.
  - Cellularity
  - Cell size distribution
  - Cytoplasm ratio



- Diffusion is modeled by a random walk of the particles:
  - Random walk (RW) ⟶ Gaussian
  - Continuous time random walk (CTRW) ⟶ Non-Gaussian

* Sugahara, et al., JMRI, 1999. *Gauvain et al, AJR, 2001.

From RW to CTRW

- In Gaussian RW theory,
  - jump length (Δx) variance and
  - waiting time between jump lengths (Δt) are finite and Gaussian.

$$\frac{\partial P(x,t)}{\partial t} = D\frac{\partial^2 P(x,t)}{\partial |x|^2} \xrightarrow{\text{solution}} s(q,\bar{\Delta}) = \exp(-D_{1,2}|q|^2\bar{\Delta})$$

- In non-Gaussian CTRW theory,
  - jump length variance and
  - waiting time between jump lengths are not constrained by Gaussian distribution.

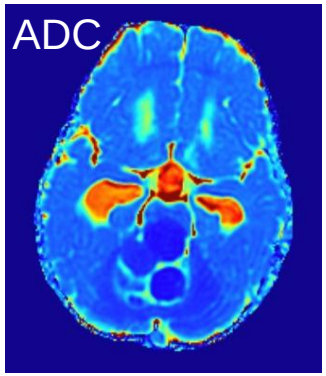
$${}_0^C D_t^{\alpha}\left(P(x,t)\right) = D_{\alpha,\beta}\frac{\partial^{2\beta} P(x,t)}{\partial |x|^{2\beta}} \xrightarrow{\text{solution}} s(q,\bar{\Delta}) = E_{\alpha}\left(-D_{\alpha,\beta}|q|^{2\beta}\bar{\Delta}^{\alpha}\right)$$

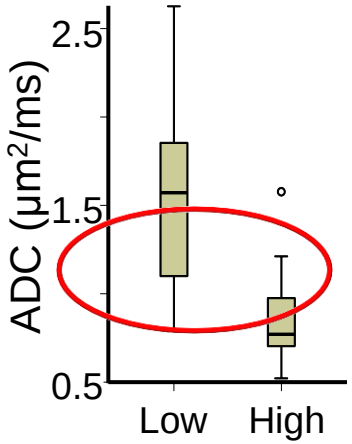
ADC Approach

- Apparent Diffusion Coefficient (ADC) values are computed from the mono-exponential model.
  - Gaussian model
  - Diffusion signal is modeled by

$$s(b) = s_0 \, exp(-bD)$$

- ADC in tumors*
  - High-grade tumors have lower ADC compared to low-grade tumors.
  - Significant overlap between groups can compromise the specificity for differential diagnosis.

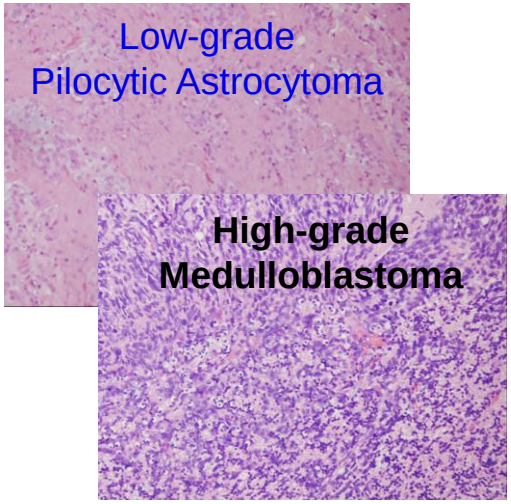




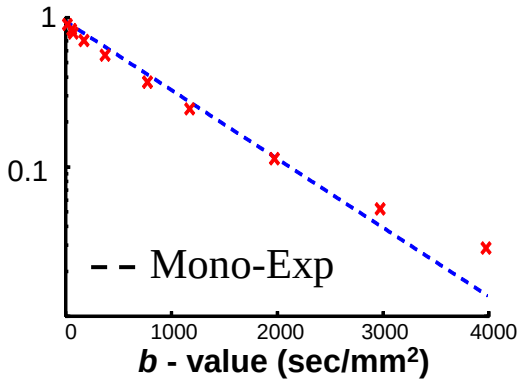
* Maier, et al., NMR Biomed, 2010. ** Rumboldt, et al., AJNR, 2006.

Limitations of ADC Approach

- Diffusion in complex heterogeneous tissues is non-Gaussian*.
  - High-grade brain tumors have more complex and heterogeneous structures than low-grade ones.



- Signal attenuation in brain tissues can not be well described by a mono-exponential decay, as predicted by the Gaussian diffusion model**.



$$s(b) = s_0\, exp(-bD)$$

* Le Bihan, Phys. Med. Biol., 2007. ** Kwee, NMR Biomed, 2010. **Cohen, NMR Biomed., 2002.

Non-Gaussian Diffusion Models

- Bi-exponential, stretched-exponential, statistical, *q*-space, kurtosis, continuous time random walk (CTRW) models, etc.
- CTRW model*

$$ {}_{0}^{C}D_{t}^{\alpha}\left(P(x,t)\right) = D_{\alpha,\beta}\frac{\partial^{2\beta}P(x,t)}{\partial|x|^{2\beta}} \xrightarrow{\text{solution}} s = s_0 E_{\alpha}\left[-(bD_m)^{\beta}\right] $$

  - D_m : diffusion coefficient, similar to ADC
  - α : fractional power of the waiting time
  - β : fractional power of the jump length

- CTRW model has been examined on healthy fixed rat brain**, but not yet in a clinical human study.

* Magin, et al., JMR, 2008. * Zhou, et al., MRM, 2010. ** Ingo et al., MRM, 2013

Objective

- To investigate the feasibility of using CTRW parameters (D_m, α, and β) to differentiate low- and high-grade tumors.

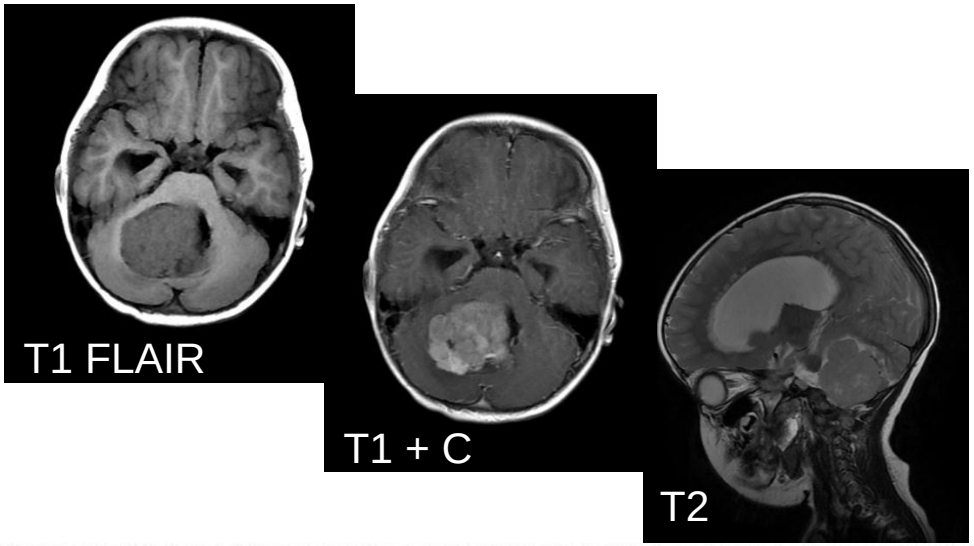
- To compare the outcomes of the differentiation by CTRW parameters and the conventional ADC value.

Patient Group

- 54 patients with histopathologically proven brain tumors
  - 38 males, 16 females
  - Age range: 4 months − 13 years
  - 24 low-grade
    - 15 WHO grade I, e.g. Pilocytic Astrocytoma
    - 9 WHO grade II, e.g. Diffuse Astrocytoma
  - 30 high-grade
    - 2 WHO grade III, e.g. Anaplastic Ependymoma
    - 28 WHO grade IV, e.g. Medulloblastoma

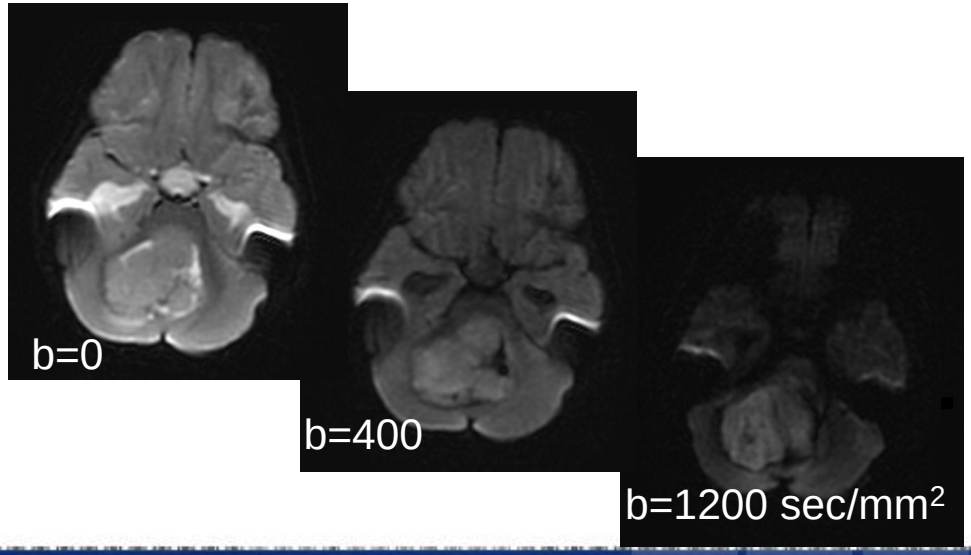
Imaging Protocol

- Image Acquisition
  - GE 3T MR scanner
  - T1-FLAIR, T1+C, T2
    - Matrix = 256 × 256

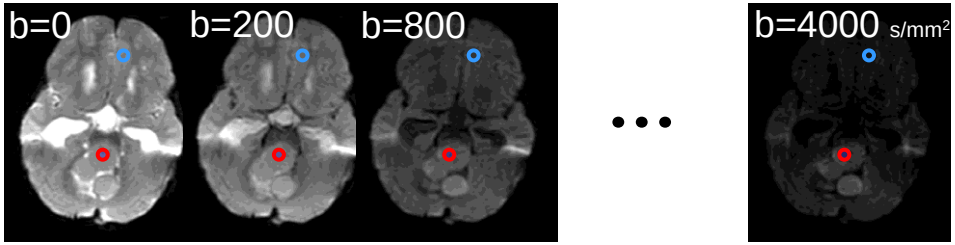


Imaging Protocol

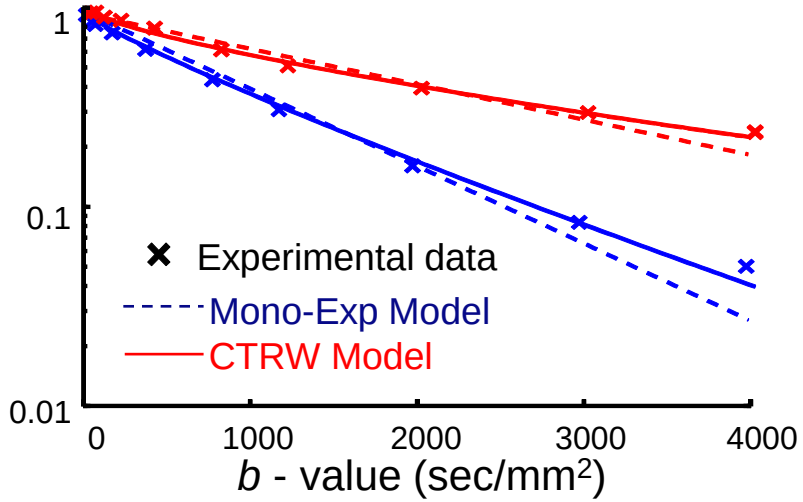
- Image Acquisition
  - GE 3T MR scanner
  - T1-FLAIR, T1+C, T2
    - Matrix = 256 × 256
  - Diffusion weighted imaging
    - 12 *b*-values = 0 ~ 4000 s/mm^2
    - TR/TE = 4700/100 ms
    - Slice thickness = 5 mm
    - Δ = 38.6 ms, δ = 32.2 ms
    - 1 average
    - FOV = 22 cm × 22 cm
    - Matrix size = 128 ×128
    - Scan time = 3 min



Data Analysis



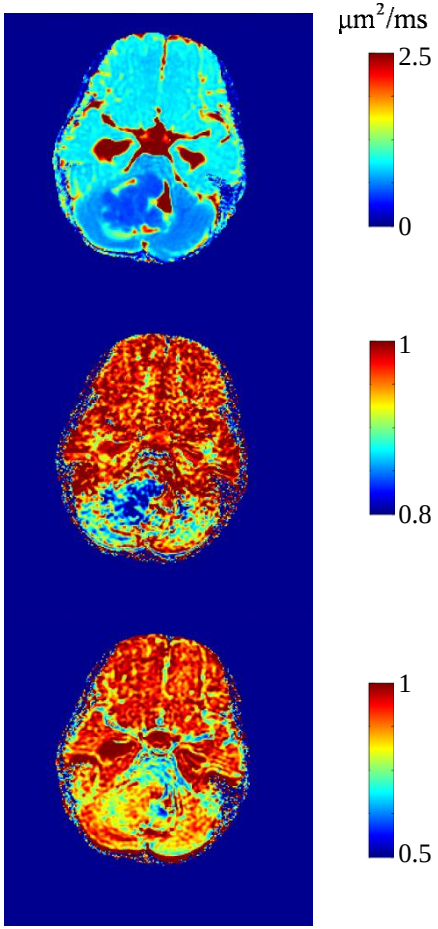
$$s = s_0 E_\alpha\left[-(bD_m)^\beta\right]$$



D_m

α

β



$b = (gG_z d)^2 (D - d/3)$

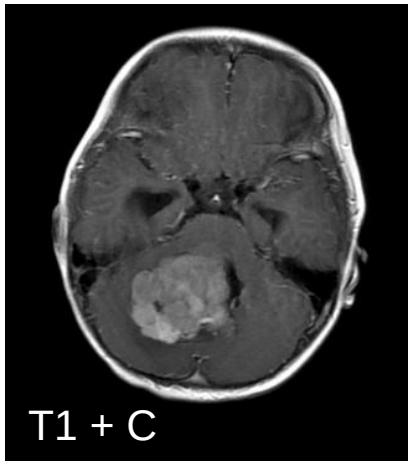
D = diffusion time

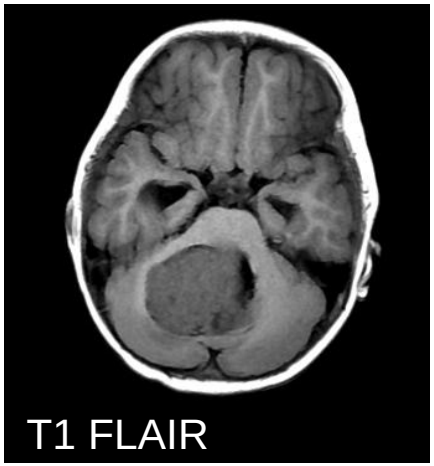
d = diffusion gradient duration

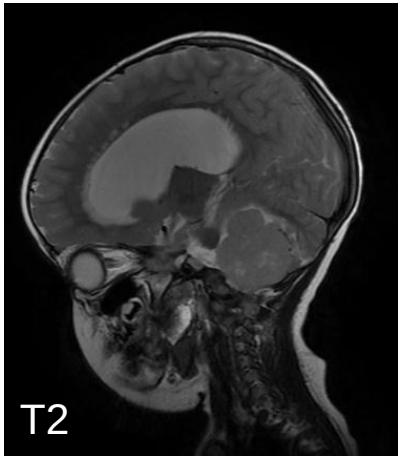
G_z = diffusion gradient amplitude

Data Analysis

- Tumor ROI Determination
  - Whole tumor coverage
  - Guided by T1 + C, T1 FLAIR, T2 images.
  - Areas of necrosis, cyst, hemorrhage, edema and calcification were avoided.

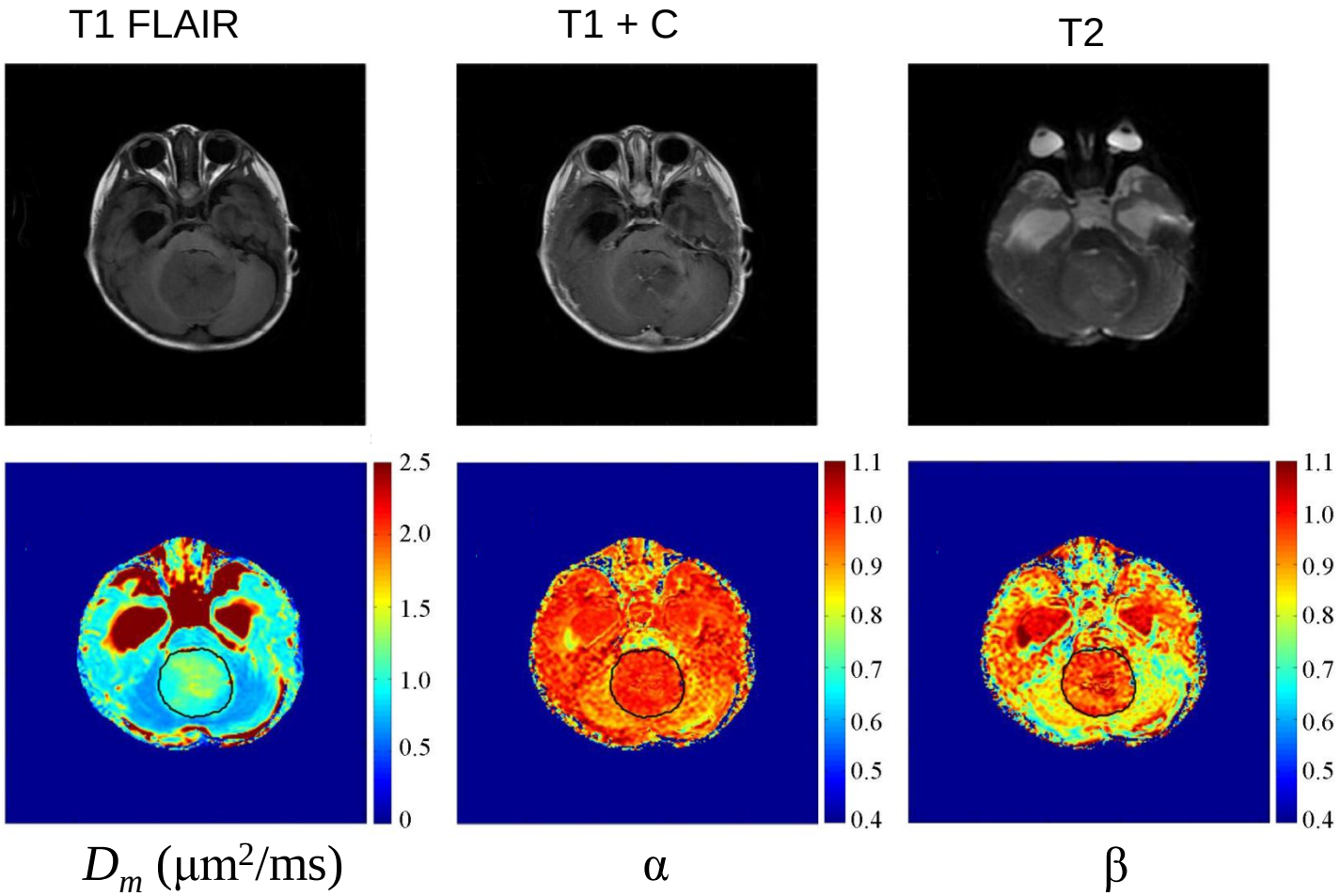






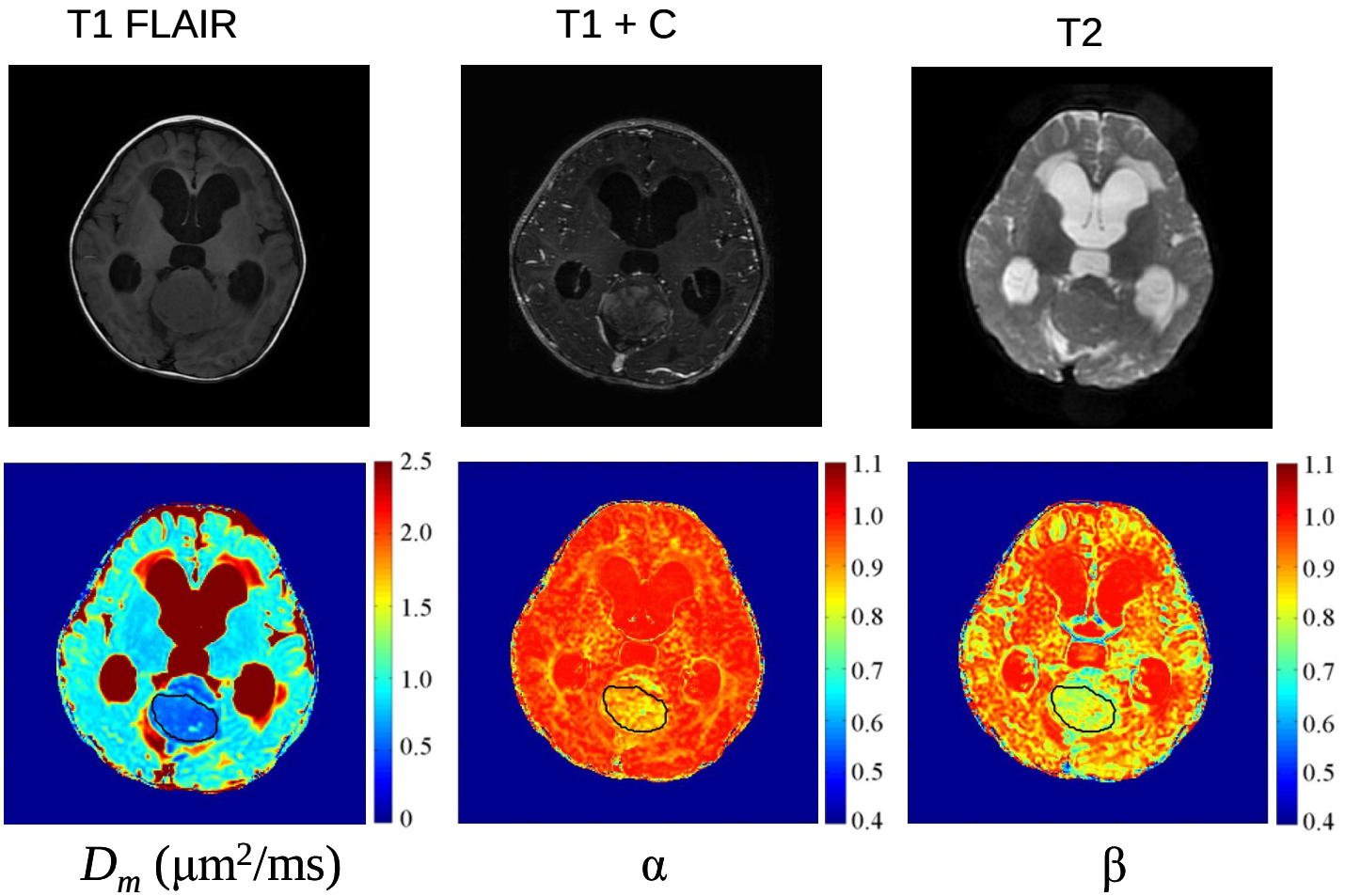
Examples of D_m, α, *and* β Maps

Low-grade (WHO II - 17m)
Ependymoma

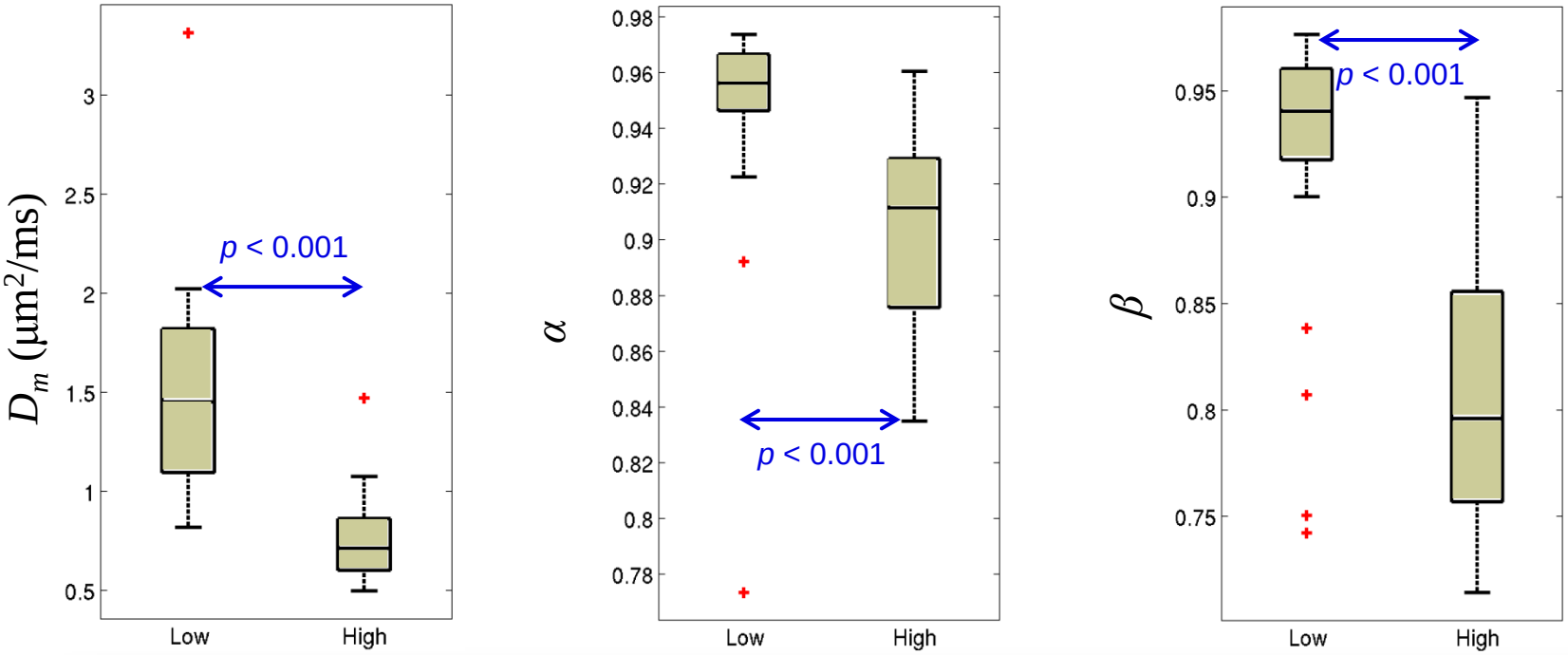


Examples of D_m, α, *and* β Maps

High-grade (WHO IV - 18m)
Medulloblastoma



Mean Values of CTRW Parameters



	D_m (μm²/ms)	α	β
Low-grade	1.50±0.50	0.95±0.04	0.92±0.07
High-grade	0.75±0.20	0.90±0.03	0.81±0.06
p value*	<0.001	<0.001	<0.001

*Mann-Whitney U test

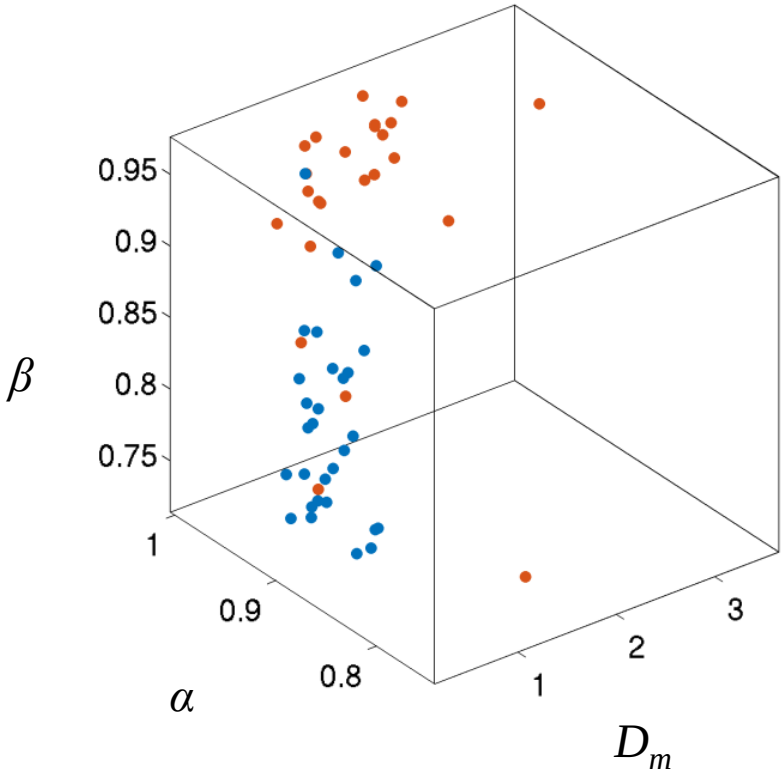
k-means Clustering Analysis

- Tumor grade classification
  - Low-grade vs. High-grade
- Multivariate analysis using D_m, α, and β
- Partition
  - *n* observations $\longrightarrow$ (D_m, α, β) estimates from 54 patients.
  - into *k* = 2 distinct groups $\longrightarrow$ low-grade and high-grade

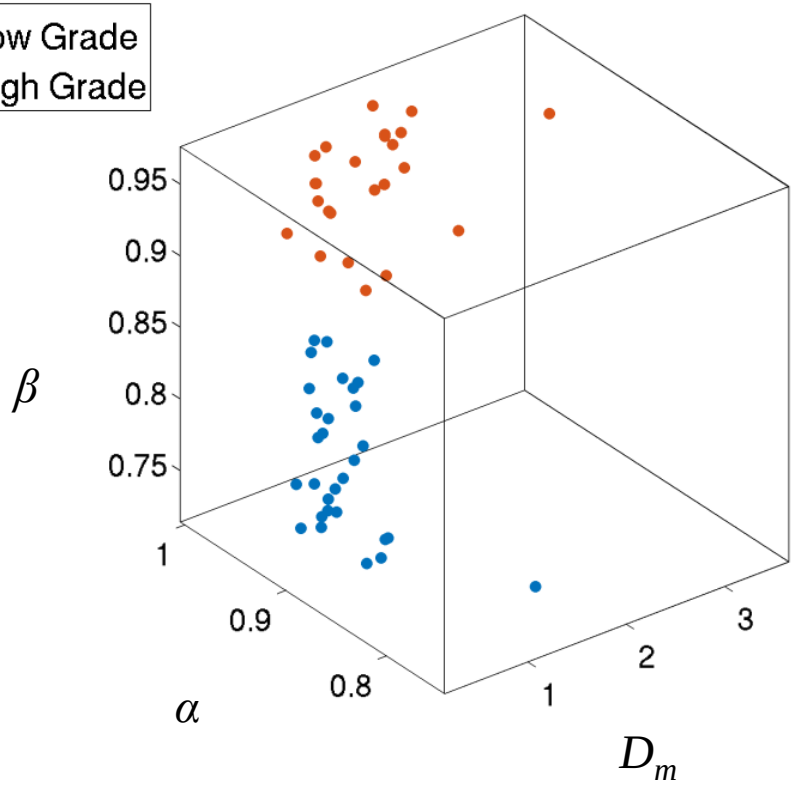
  so that observations within a group are similar.

3D Scatter Plots

Mean CTRW parameter values
(using gold standard)



k-means clustering analysis
(blind analysis)



Performance Analysis

- Analysis was performed
  - by using the tumor differentiation results from the *k*-means clustering
  - by using the histopathology as a reference.

	Monoexponential (ADC)	CTRW (D_m, α, β)
Sensitivity	0.93	0.87
Specificity	0.54	0.83
Accuracy	0.75	0.85

Conclusion

- CTRW parameters can be significantly different between the low-grade and high-grade pediatric brain tumors.
- The combination of CTRW parameters produced better accuracy and specificity than the ADC values obtained from the monoexponential model.
- The CTRW model can provide quantitative imaging markers to improve diagnosis of pediatric brain tumors.

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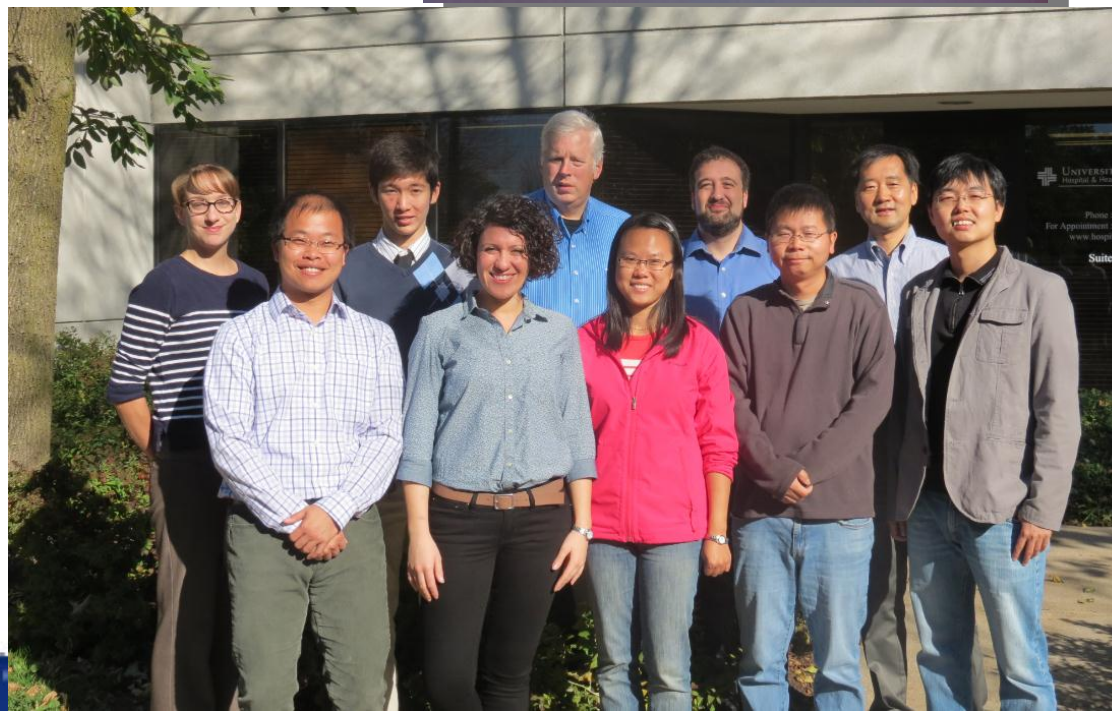
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