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Quantitative Assessment of Diffusional Kurtosis Anisotropy

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Abstract

Diffusional kurtosis imaging (DKI) measures the diffusion and kurtosis tensors to quantify restricted, non-Gaussian diffusion that occurs in biological tissue. By estimating the kurtosis tensor, DKI accounts for higher order diffusion dynamics, when compared to diffusion tensor imaging (DTI), and consequently, it can describe more complex diffusion profiles. Here, we compare several measures of diffusional anisotropy which incorporate information from the kurtosis tensor, including kurtosis fractional anisotropy (KFA) and generalized fractional anisotropy (GFA), to the diffusion-tensor derived fractional anisotropy (FA). KFA and GFA demonstrate a net enhancement relative to FA when multiple white matter fiber bundle orientations are present in both simulated and human data. In addition, KFA shows net enhancement in deep brain structures, such as the thalamus and the lenticular nucleus where FA indicates low anisotropy. Thus, KFA and GFA provide additional information relative to FA regarding diffusional anisotropy and may be particularly advantageous for assessing diffusion in complex tissue environments.

Keywords

DKI; Kurtosis; anisotropy; FA; KFA; GFA; diffusion; non-Gaussian

Introduction

Diffusion anisotropy measures are common for quantifying properties of tissue microstructure from diffusion MRI data. Among them, fractional anisotropy (FA) is the most widely used (1,2). However, FA has the shortcoming that it may take on small values, or in principle even vanish, despite the diffusion dynamics having significant angular dependence, for example, in white matter (WM) regions with multiple fiber bundle orientations (2-4). In addition, FA has been shown to be sensitive to partial volume effects

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(5-9) and the orientation dispersion of neurites (10). For these reasons, it may be of interest to consider additional measures of diffusional anisotropy.

Since the introduction of diffusional kurtosis imaging (DKI) (11,12), investigators have proposed several anisotropy measures based on the kurtosis tensor (13-15). Some of these measures also incorporate information from the diffusion tensor and are therefore not directly analogous to FA for measuring anisotropy (13,14). However, a novel measure of anisotropy was recently proposed, which is purely a property of the kurtosis tensor and can be regarded as a natural extension of the FA concept to the kurtosis tensor (15). Here, we have termed this measure of anisotropy kurtosis fractional anisotropy (KFA) and demonstrate that it provides distinct and complementary information about diffusional anisotropy when compared to FA.

In addition, generalized fractional anisotropy (GFA) (16) can be calculated from the diffusion and kurtosis tensors via the DKI-derived approximation of the diffusion orientation distribution function (dODF). Like FA, GFA can be interpreted as the degree of preferential directional diffusion mobility, with the benefit of being able to accommodate more complex diffusion profiles.

The main purpose of this paper is to describe and motivate the application of KFA and GFA, which can both be calculated directly from DKI datasets. In addition, we illustrate distinct features of KFA by comparing it with FA and alternative kurtosis-based measures of anisotropy for both numerical simulations and for in vivo human data.

Theory

Diffusional Kurtosis Imaging

To characterize anisotropic, non-Gaussian diffusion dynamics, DKI assumes that the diffusion-weighted signal can be well described by the fourth-order cumulant expansion of the diffusion signal, provided the b-value (the strength of diffusion weighting) is not too large. The natural logarithm of the diffusion signal is thus given by (11,12):

$$\ln S(b, \hat{n}) = \ln S_0 - b \sum_{ij} n_i n_j D_{ij} + \frac{b^2 \bar{D}^2}{6} \sum_{ijkl} n_i n_j n_k n_l W_{ijkl} \quad [1]$$

Where b is the b-value, $\hat{n}$ is a normalized direction vector, with the hat symbol indicating a unit vector, S_0 is the signal with no diffusion weighting, $\mathbf{D}$ is the diffusion tensor, $\bar{D}$ is the mean diffusivity, $\mathbf{W}$ is the kurtosis tensor, the subscripts label Cartesian components, and sums on the indices are carried out from 1 to 3.

Directional diffusivity and diffusional kurtosis estimates for an arbitrary direction are thus given by:

$$D(\hat{n}) = \sum_{ij} n_i n_j D_{ij}, \quad [2]$$

and

$$K(\hat{n}) = \frac{\bar{D}^2}{D(\hat{n})^2} \sum_{ijkl} n_i n_j n_k n_l W_{ijkl}. \quad [3]$$

Then, mean diffusivity and diffusional kurtosis are calculated as the mean directional diffusivity and kurtosis over all directions:

$$\bar{D} = \frac{1}{4\pi} \int d\hat{n} D(\hat{n}), \quad [4]$$

and

$$\bar{K} = \frac{1}{4\pi} \int d\hat{n} K(\hat{n}). \quad [5]$$

We note that the calculation of $\bar{K}$ requires knowledge of both the diffusion and kurtosis tensors. However, it is possible to calculate the mean of the kurtosis tensor by letting:

$$W(\hat{n}) = \sum_{ijkl} n_i n_j n_k n_l W_{ijkl}. \quad [6]$$

Then,

$$\bar{W} = \frac{1}{4\pi} \int d\hat{n} W(\hat{n}). \quad [7]$$

Both $\bar{D}$ and $\bar{W}$ can be computed readily from $\mathbf{D}$ and $\mathbf{W}$ by $\bar{D} = \text{Tr}(\mathbf{D})/3 = (\lambda_1 + \lambda_2 + \lambda_3)/3$,

where $\text{Tr}(\cdots)$ is the trace operator and λ_1 , λ_2 , and λ_3 are the three eigenvalues of the diffusion tensor, and (15):

$$\bar{W} = (W_{1111} + W_{2222} + W_{3333} + 2W_{1122} + 2W_{1133} + 2W_{2233})/5. \quad [8]$$

It should be noted that $\bar{W}$ approximates $\bar{K}$, but they are only strictly equal in the case where the diffusion tensor is isotropic, as:

$$\bar{K} = \frac{1}{4\pi} \int d\hat{n} \frac{\bar{D}^2}{D(\hat{n})^2} W(\hat{n}). \quad [9]$$

Diffusion Orientation Distribution Function

An additional novel feature of DKI in comparison to DTI is its ability to directly resolve multiple fiber bundle orientations in voxels with a non-uniform fiber bundle distribution. To accomplish this, DKI evaluates the dODF (17,18), which is a commonly used function to

extract directional information from diffusion MRI data (16-24). The dODF evaluates the radial projection of the diffusion displacement probability density function (dPDF) along a given direction in space to quantify the relative degree of diffusion mobility along that direction, without making any explicit assumptions about tissue microstructure, by:

$$\psi_{\alpha}(\hat{\mathbf{n}}) = \frac{1}{Z} \int_0^{\infty} ds s^{\alpha} P(s\hat{\mathbf{n}}, t), \quad [10]$$

where s is the displacement, $P(s\hat{\mathbf{n}}, t)$ is the dPDF, the radial weighting power, α , increases the sensitivity to relatively long diffusion displacements for $\alpha > 0$, and Z is the normalization constant.

Since the diffusion and kurtosis tensors are fully symmetric, the dODF is symmetric with respect to the origin. Thus, local maxima pair in the dODF indicate orientations with overall less restricted diffusion and are interpreted as distinct fiber bundle orientations. By accounting for the leading effects of non-Gaussian diffusion, the kurtosis dODF can resolve angular differences in the dPDF, which are not apparent from analysis of the diffusion tensor alone (18).

Fractional Anisotropy

Fractional anisotropy (FA) is the most commonly used measure of diffusion anisotropy taken from the diffusion tensor. The original concept behind FA is to decompose the diffusion tensor into isotropic and anisotropic tensors, $\mathbf{D} = \mathbf{D}\mathbf{I}^{(2)} + (\mathbf{D} - \mathbf{D}\mathbf{I}^{(2)})$, where $\mathbf{I}^{(2)}$ is the fully symmetric, second order isotropic tensor defined by its components, $I_{ij}^{(2)} = \delta_{ij}$, where δ_{ij} is the Kronecker delta. Then, FA is the ratio of the magnitudes of the anisotropic component and the diffusion tensor (1):

$$FA \equiv \sqrt{\frac{3}{2}} \cdot \frac{\|\mathbf{D} - \mathbf{D}\mathbf{I}^{(2)}\|_F}{\|\mathbf{D}\|_F}, \quad [11]$$

where the normalization constant $\sqrt{3/2}$ is included so that FA values range from 0 to 1, and $\|\cdots\|_F$ indicates the Frobenius norm for a tensor $\mathbf{A}$ of rank N :

$$\|\mathbf{A}\|_F \equiv \sqrt{\sum_{i_1, i_2, \dots, i_N} (A_{i_1, i_2, \dots, i_N})^2}. \quad [12]$$

We note that the special case of $N = 1$ simply corresponds to the standard Euclidian vector norm, and the Frobenius norm is manifestly invariant under rotations.

This definition of FA can be rewritten into the conventional form by incorporating the relationships between the eigenvalues and the Frobenius norm of the diffusion tensor (1):

$$FA = \sqrt{\frac{3}{2}} \cdot \frac{\sqrt{(\lambda_1 - \bar{D})^2 + (\lambda_2 - \bar{D})^2 + (\lambda_3 - \bar{D})^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}. \quad [13]$$

Kurtosis Anisotropy

One method for examining anisotropy in the kurtosis tensor proposed by Hui et al. (13) is to sample directional kurtosis along the diffusion tensor eigenvectors $\mathbf{v}_i$ corresponding to each eigenvalue λ_i , such that $K_i = K(\mathbf{v}_i)$, and then define kurtosis anisotropy (KA) with an analogous equation:

$$KA_\lambda = \sqrt{\frac{3}{2}} \cdot \frac{\sqrt{(K_1 - K)^2 + (K_2 - K)^2 + (K_3 - K)^2}}{\sqrt{K_1^2 + K_2^2 + K_3^2}}, \quad [14]$$

where $K = (K_1 + K_2 + K_3)/3$. One motivation for this definition is that in WM regions, the eigenvectors of the diffusion tensor estimate orientations which are parallel and perpendicular to the orientation of a WM fiber bundle, where diffusion displacement is expected to be minimally and maximally restricted. However, this definition is not analogous to the original definition of FA, and by applying a rank 2 diffusion tensor property to the rank 4 kurtosis tensor, it cannot reliably capture the full anisotropy in the kurtosis tensor. This observation prompted Poot et al. to propose an additional measure of KA (14):

$$KA_\sigma = \sqrt{\frac{1}{4\pi} \int d\hat{n} (K(\hat{n}) - \bar{K})^2}, \quad [15]$$

which measures the standard deviation of the directional kurtosis. Although KA_σ evaluates variability of directional kurtosis measures, it is not normalized to a range of 0 to 1, as it scales with the magnitude of diffusional kurtosis, and it does not directly parallel the original definition of FA.

As noted above, $\bar{W}$ approximates $\bar{K}$ with the correspondence becoming exact for isotropic diffusion. So another possible measure of anisotropy taken from the diffusion and kurtosis tensors is given by:

$$KA_\mu = \left| 1 - \frac{\bar{W}}{\bar{K}} \right|, \quad [16]$$

Where $|\cdots|$ is the absolute value. It is of interest to investigate differences in $\bar{W}$ and $\bar{K}$ as $\bar{W}$ can be estimated from as few as 9 diffusion encoding directions, thereby significantly reducing the data acquisition time (15).

KA_λ , KA_σ , and KA_μ incorporate information from both the diffusion and kurtosis tensors and are thus not pure measures of kurtosis tensor anisotropy. However, generalizing the original definition of FA to the kurtosis tensor is straightforward, and one finds (15):

$$KFA = \frac{\|\mathbf{W} - \overline{\mathbf{W}}\mathbf{I}^{(4)}\|_F}{\|\mathbf{W}\|_F}, \quad [17]$$

where $\mathbf{I}^{(4)}$ is the fully symmetric, rank 4 isotropic tensor defined by its components:

$$I_{ijkl}^{(4)} = \frac{1}{3}(\delta_{ij}\delta_{kl} + \delta_{ik}\delta_{jl} + \delta_{il}\delta_{jk}). \quad [18]$$

As with FA, the normalization is chosen so that KFA values range from 0 to 1. When $\|\mathbf{W}\|_F = 0$, then Eq. [17] is indeterminate, but one can define this case to have $KFA = 0$.

The kurtosis and diffusion tensors are distinct physical quantities that encode different aspects of the diffusion dynamics (12). As a consequence, they can vary independently and in principle have no definite relationship to each other. The FA and KFA are thus also distinct quantities, either of which may vanish when the other is nonzero. Hence, they should be regarded as complementary rather than redundant metrics of diffusion anisotropy.

Generalized Fractional Anisotropy

A more comprehensive measure of diffusion anisotropy calculates anisotropy over the dODF as opposed to measures obtained directly from the diffusion or kurtosis tensors. Eq. [13] can be extended to the dODF to define the generalized fractional anisotropy (GFA) by (16):

$$GFA = \frac{std(\psi_\alpha)}{rms(\psi_\alpha)}, \quad [19]$$

where $std(\psi_\alpha)$ is the standard deviation of ψ_α and $rms(\psi_\alpha)$ is the root mean square of ψ_α , computed over all orientations, $\mathbf{n}$. We note that $std(\psi_\alpha)$ is zero for isotropic diffusion, and $rms(\psi_\alpha)$ is always greater or equal to than $std(\psi_\alpha)$, with the ratio increasing as the standard

deviation, increases, i.e. as the difference between $\langle \psi_\alpha^2 \rangle$ and $\langle \psi_\alpha \rangle^2$ increases, where the angle brackets, $\langle f \rangle$, are used to indicate the average over all values of a continuous function, f . Thus, GFA values range from 0 to 1 indicating zero to maximal anisotropy in the dODF. Similar in spirit to both FA and KFA, GFA normalizes the angular variability in the dODF by its magnitude in order to quantify the angular dependence of diffusion mobility.

The closed form solution to the kurtosis dODF has recently been derived (18). Thus GFA can be readily calculated from the diffusion and kurtosis tensors to indicate the anisotropy in the dODF. We calculate GFA as:

$$GFA = \sqrt{1 - \frac{\langle \psi_{\alpha,K} \rangle^2}{\langle \psi_{\alpha,K}^2 \rangle}}, \quad [20]$$

which follows directly from Eq. [19], where $\psi_{\alpha,K}$ is the kurtosis dODF approximation. It should be noted that the GFA depends both on the approximation used for the dODF (e.g., kurtosis or q-ball) and on the choice of the radial weighting power, α . In this study, we used the kurtosis dODF with $\alpha = 4$ (18).

Methods

Multiple Gaussian Compartment Model

To illustrate differences in the anisotropy metrics, we consider some simple examples for a multiple, Gaussian compartment model having M , non-exchanging compartments, with each compartment having the water fraction f_m and a compartmental diffusion tensor, $\mathbf{D}^{(m)}$. The diffusion and kurtosis tensors can then be obtained as combinations of the diffusion tensors from each compartment by (17):

$$\mathbf{D} = \sum_{m=1}^N f_m \mathbf{D}^{(m)}, \quad [21]$$

and,

$$W_{ijkl} = \frac{1}{D^2} \left\{ \left[\sum_{m=1}^N f_m \left(D_{ij}^{(m)} D_{kl}^{(m)} + D_{ik}^{(m)} D_{jl}^{(m)} + D_{il}^{(m)} D_{jk}^{(m)} \right) \right] - D_{ij} D_{kl} - D_{ik} D_{jl} - D_{il} D_{jk} \right\}. \quad [22]$$

For this model (11,12):

$$W(\hat{\mathbf{n}}) = 3 \frac{\delta^2 D(\hat{\mathbf{n}})}{D^2}, \quad [23]$$

where,

$$\delta^2 D(\hat{\mathbf{n}}) \equiv \sum_{m=1}^N f_m \left\{ [D^{(m)}(\hat{\mathbf{n}}) - D(\hat{\mathbf{n}})]^2 \right\}, \quad [24]$$

is the variance of the diffusion coefficient, illustrating that the kurtosis tensor reflects overall heterogeneity in the diffusion environment.

Because we are interested in measuring differences in isotropic and anisotropic diffusion, we consider combinations of cylindrically symmetric, anisotropic tensors, defined with eigenvalues of $\lambda = [\lambda_{||}, \lambda_{\perp}, \lambda_{\perp}]$, where $\lambda_{||}$ is the parallel or principal eigenvalue and $\lambda_{\perp}$ are the perpendicular eigenvalues, which represent idealized Gaussian diffusion in WM fiber bundles, and the rank 2 isotropic tensor, $I^{(2)}$, ($FA = 0$), which may, for example, represent unrestricted diffusion in cerebrospinal fluid.

To evaluate the effects of changing the ratio of $\lambda_{\parallel}$ and $\lambda_{\perp}$ on each of the parameter estimates, we vary $\lambda_{\perp}$ while keeping $\lambda_{\parallel}$ set at $1.7 \mu\text{m}^2/\text{ms}$ for a single diffusion compartment, $\mathbf{D}_1$. Because this represents idealized Gaussian diffusion with zero kurtosis, diffusional heterogeneity is increased by adding a second, equivalently oriented compartment, $\mathbf{D}_2 = 2\mathbf{D}_1$, resulting in a non-zero kurtosis tensor. To evaluate the effects of crossing fibers on anisotropy measures, we consider examples with 2 or 3 crossing fiber bundles with $\lambda = [1.7, 0.3, 0.3] \mu\text{m}^2/\text{ms}$ and separation angles between the principal eigenvectors ranging between 1 and 90 degrees. For simplicity, we consider compartments with equal water fractions.

To avoid numerical artifacts, directional kurtosis estimates used to calculate KA_{λ} are regularized by setting $K(\mathbf{n}) = 1 \times 10^{-9}$ when $K(\mathbf{n}) < 1 \times 10^{-9}$. In addition, in the case where the crossing angle between multiple fiber bundles is 90° , the eigenvectors of the diffusion tensor are degenerate. So to avoid random variation in KA_{λ} , the vectors used to evaluate $K(\lambda_i)$ are fixed to their values with a 89° crossing angle.

Data Acquisition

DKI datasets were acquired for 5 healthy, adult volunteers ranging in age from 27 to 53, with a 3T TIM Trio MRI scanner (Siemens Medical, Erlangen, Germany) using a vendor-supplied diffusion sequence, 3 b-values of 0, 1000, and 2000 s/mm^2 , and 64 isotropically distributed gradient directions to estimate the diffusion and kurtosis tensors. Acquisition parameters used were TR = 7200 ms, TE = 103 ms, voxel dimensions = $2.5 \times 2.5 \times 2.5 \text{ mm}^3$, matrix size $\times$ number of slices = $88 \times 88 \times 52$, parallel imaging factor of 2, bandwidth = 1352 Hz/Px, and a 32 channel head coil with adaptive combine mode. To estimate inter- and intra-subject variability, 3 independent DKI datasets and a total of 25 images with no diffusion weighting (b0 images) were acquired for each subject. Each independent DKI acquisition took 16 min, and the full DKI acquisition with a total of 25 b0 images took 51 min. An additional MPRAGE sequence was also acquired for each subject for anatomical reference.

Image Analysis

To correct for subject motion, all b0 images for each subject were co-registered to the subject's first b0 image using SPM8 (Wellcome Trust Center for Neuroimaging, London, UK) with an affine, rigid body transformation with the normalized mutual information cost function and trilinear interpolation. In the case where the co-registered b0 image came from an independent DKI acquisition, the rigid-body transformation was also applied to all DWIs of that dataset. An average DKI dataset was then created by averaging all 25 independent b0 images and all 3 independent images for each applied diffusion encoding gradient. Unless otherwise stated, all analyses were performed on the average DKI dataset from each subject.

DKI processing was performed by a previously described method using Gaussian smoothing with a full-width at half maximum of 1.25 times the voxel dimensions to minimize the effects of noise and misregistration, and tensor fitting was then performed using a constrained linear least squares algorithm (25). Since our analyses included independent DKI datasets with only one b0 image, $\ln(S_0)$ was included as an unknown parameter to be

estimated resulting in a total of 22 unknown parameters to be determined. The kurtosis dODF was evaluated using in-house software. Because the kurtosis dODF is symmetric with respect to the origin, we evaluate it for 1281 points, defined by tessellation of the icosahedron (16), over exactly one half of a spherical shell, resulting in approximately 4.3 degrees between each point and its nearest neighbors. The orientation of each local maxima pair was estimated by an exhaustive grid search over these 1281 points followed by the non-linear quasi-Newton method for iterative optimization. GFA was calculated by evaluating the kurtosis dODF over each of these points, and the number of fiber directions (NFD) was estimated by the total number of local maxima pair detected from the kurtosis dODF in each voxel.

Evaluating each independent DKI dataset took 27.2 ± 2.5 minutes (mean $\pm$ standard deviation) using MATLAB's parallel computing toolbox on a data server with an Intel Xeon 8-core processor.

To analyze anisotropy measures in different regions of interest (ROIs) across the 5 healthy volunteers, the FA maps from the average DKI datasets were normalized to the ICBM-DTI-81 FA WM atlas (26) using SPM8 with non-linear transformation and trilinear interpolation. The transformation for the average DKI dataset was also applied to all DKI-derived parameter maps from each DKI dataset. WM ROIs analyzed (and the number of voxels they contain, n) include the full WM ROI (n = 170,006) corpus callosum (CC) (n = 35,291), cingulum bundle (CB) (n = 5,093), superior longitudinal fasciculus (SLF) (n = 13,212), and corona radiata (CR) (n = 36,151). We also created gray matter ROIs for the lenticular nucleus (LN) (n = 6,815), which consists of the globus pallidus and the putamen of the basal ganglia, and the thalamus (Thal) (4,293). The LN was defined bilaterally as the area between the internal capsule (IC) and the external capsule (EC) in the WM template. The Thal was manually segmented using the WM template overlaid on the T2-weighted template image, to be at or above the level of the splenium of the CC, lateral to the lateral ventricles, and medial to the IC.

To assess the variability in parameter estimates, voxel-wise mean and standard deviation, inter-subject variability (26,27), and intra-subject variability (27,28) within each of the ROIs from the normalized datasets were analyzed. The mean and standard deviation values were pooled from the voxels within each ROI from DKI datasets of all 5 subjects. To calculate inter-subject variability, a voxel-wise coefficient of variation map was created across all 5 subjects, and the mean and standard deviation of the inter-subject variability map were calculated for each ROI. To calculate intra-subject variability, a voxel-wise coefficient of variation map was calculated (28) across the 3 independent acquisitions for each subject. The average and standard deviation from the 5 intra-subject variability maps were pooled from the ROIs applied to all subjects.

To highlight differences between the anisotropy parameters, parameter difference maps are calculated as the difference between selected parameters of interest. To emphasize the average group difference in the anisotropy parameters, these maps are generated from the mean of the normalized parameter maps across all subjects. The normalized NFD maps are

also averaged across all subjects to illustrate the number of fiber directions detected within the group.

Results

To illustrate differences in quantitative measures of diffusion anisotropy, all anisotropy measures are evaluated from simulated data with the multiple Gaussian compartment model in Fig. 1 for a single diffusion orientation with non-zero kurtosis and in Figs. 2 and 3 for 2 and 3 crossing WM fiber bundles, respectively.

In Fig. 1, increasing $\lambda_{\perp}$ relative to $\lambda_{\parallel}$ decreases FA, GFA, and KFA. In the case with only anisotropic diffusion, this has no effect on KA_{λ} or KA_{σ} since the directional kurtosis is constant, $K(\mathbf{n}) = 1/3$, resulting in $KA_{\lambda} = 0$ and $KA_{\sigma} = 0$. KA_{μ} decreases as diffusional anisotropy decreases. Adding an isotropic compartment decreases both FA and KFA, but causes a slight increase in KFA by increasing variability in the directional diffusional heterogeneity. The addition of isotropic diffusion has variable effects on the other kurtosis anisotropy parameters.

In Figs. 2 and 3, FA is reduced for fiber bundle orientations at high crossing angles and vanishes for the 3 fiber bundle example with a 90° crossing angle. KFA, on the other hand, is less sensitive to the crossing angle in cases where there is no isotropic diffusion, but shows a dip at a particular crossing angle as the relative magnitude of the contributions from the isotropic and anisotropic compartments to the diffusional heterogeneity are reversed. For the case with 2 anisotropic WM fiber bundles and no isotropic diffusion (Figure 2A), KFA is constant, and it can be evaluated explicitly as $KFA = \sqrt{13/15}$. A mathematical derivation of this result is included in the Appendix to further explore the effects of the adjustable parameters on the kurtosis tensor and to highlight differences between KFA and FA. The overall shape of the dODF most accurately depicts the simulated fiber bundle orientation across all crossing angles, thus for this model, GFA may be the most accurate measure quantifying preferential diffusion mobility in regions with crossing fibers. In Fig. 2A, KA_{λ} is zero, resulting from regularization, as the eigenvalues of the diffusion tensor point to directions with approximately zero diffusional kurtosis. KA_{σ} scales with the magnitude of the mean diffusional kurtosis, so in Figs. 2A and 3A, KA_{σ} vanishes at small crossing angles, as the overall diffusion dynamics with this model become increasingly Gaussian. The magnitude of KA_{μ} is typically small, particularly in cases with no isotropic diffusion, but for this particular model, when there at low crossing angles and isotropic diffusion, KA_{μ} can be appreciatively large.

Representative parameter maps for the 6 different anisotropy measures from a single healthy volunteer are given in Fig. 4. In general, GFA is greater than FA, but the two values are closely correlated. KFA shows similar enhancement as FA in WM regions that are expected to show diffusional anisotropy. However, KFA also shows enhancement in gray matter regions such as the Thal and LN where FA values are relatively low. In addition, KFA shows enhancement in regions between the CC and CB, which could demonstrate complex diffusion profiles due to separate contributions from these two large, well-defined fiber bundles. KA_{λ} and KA_{σ} show enhancement in regions with expected diffusional anisotropy,

but the anisotropic regions are typically narrower, particularly when compared to GFA. KA_{μ} demonstrates anisotropy in expected regions, but the values are much less than other measures of anisotropy.

The specific ROIs analyzed as well as anisotropy difference maps are shown in Fig. 5. GFA is typically greater than FA so the difference between GFA and FA is positive throughout the WM. However, this difference can be enhanced in regions where there is complex tissue architecture, as may occur in voxels with crossing WM fibers from the SLF, CR, and CC; the CC and CB; or in the pons. The difference between KFA and FA is also enhanced in these regions, particularly in the boundary regions between WM ROIs, where contributions to the overall diffusion dynamics from crossing fibers with high crossing angles can cause FA to be anomalously low. The difference between KFA and FA is also increased in deep brain structures such as the LN and Thal, where FA typically indicates low diffusional anisotropy. Crossing fiber regions detected from the kurtosis dODF are illustrated by the maps in the NFD column of Fig. 5. The difference between KFA and FA is generally enhanced in regions where NFD is greater than 1. The difference between GFA and KFA is enhanced in WM regions with high diffusional anisotropy, such as the CC. This trend is similar between FA and KFA, but the differences are significantly less.

Fig. 6 shows representative slices from the ICBM WM template as well as the group average for the normalized FA, GFA, and KFA images. The template and the average of the normalized FA images are highly similar, validating the normalization procedure. The GFA map is enhanced relative to the FA map and the WM regions identified with GFA are slightly broader. Mean and standard deviations for ROIs in these maps are summarized in Table 1. Inter- and intra-subject variability maps are given in Fig. 7. Mean and standard deviation values for these maps are given in Tables 2 and 3, respectively.

In Table 1, the standard deviation within each ROI tends to be similar for FA and KFA, but is consistently higher for GFA. Mean values are also typically higher with GFA, with the exception of the CB and LN, where KFA indicates the highest anisotropy. In Table 2, the inter-subject variability is comparable for the three anisotropy measures, but tends to be slightly increased for FA in WM ROIs relative to KFA and GFA (with the exception of KFA in the CC, which has the highest inter-subject variability). However, KFA has the highest inter-subject variability in GM ROIs. Intra-subject variability (Table 3) is consistently lower in GFA compared to FA in all ROIs, but is significantly increased in KFA relative to the other anisotropy measures.

Discussion

KFA measures anisotropy in the fourth order kurtosis tensor, is mathematically analogous to FA, and provides complementary information about anisotropy in diffusion dynamics. Other measures of anisotropy, such as KA_{λ} , KA_{σ} , and KA_{μ} measure anisotropy in diffusional kurtosis but they are not specific to the kurtosis tensor, as they also incorporate information from the diffusion tensor. It should be noted that KFA is purely a function of the kurtosis tensor and does not correspond precisely to the angular variability in the diffusional kurtosis (which depends on both the kurtosis and diffusion tensors).

GFA measures anisotropy in the dODF as a way of quantifying preferential diffusion mobility. By incorporating higher-order information from the kurtosis tensor, GFA can account for anisotropy from more complex diffusion profiles compared to FA. As a result, GFA may sometimes be a more appropriate measure of diffusional anisotropy, particularly in regions with crossing WM fiber bundles, where FA may underestimate the degree of diffusional anisotropy.

We have used multiple, non-exchanging, Gaussian compartment models as simple illustrations of the intricate relationships between the underlying diffusion dynamics and quantitative measures of diffusion anisotropy. These are particularly apparent when there are multiple anisotropic diffusion compartments with preferential diffusion occurring along different orientations, as occurs in vivo when WM fiber bundles cross. Since a single quantitative anisotropy measure cannot characterize all features of the underlying diffusion dynamics, it may be of interest to combine anisotropy measures in analysis of complex tissue architecture. We note in particular that the FA may vanish even when the diffusion is not isotropic (see, for example, Fig. 3), in which case the kurtosis anisotropies may be especially useful. In Figs. 2B and 3B there is a dip in KFA at a specific crossing angle. This occurs in this model as the crossing angle affects the overall degree of non-Gaussian diffusion in the anisotropic compartments, and at a specific crossing angle, the relative magnitude of the effects of the isotropic and anisotropic compartments to the overall diffusional heterogeneity inverts, as can be seen in the change in morphology of $W(\mathbf{n})$.

GFA tends to have greater variability relative to FA within ROIs, which may in part be due to GFA being generally elevated relative to FA (Figs. 5 and 6). However, inter- and intra-subject variability are consistently lower for GFA than FA in all ROIs, indicating a possible advantage of a more comprehensive assessment of diffusional anisotropy on parameter consistency. KFA on the other hand tends to have similar variability to FA within ROIs and between subjects. However, KFA tends to have higher variability than both FA and GFA within subjects (Fig. 7 and Tables 1-3). This is likely due to the relatively lower precision of the kurtosis tensor compared to the diffusion tensor, as it is more susceptible to the effects of signal noise from the contributions of higher order terms in the b-value and requires a higher number of unknown parameters to be estimated (30). We note that this does not result in higher within ROI variance for the KFA relative to FA on average, so signal noise may be a less significant source of error for the within ROI variance compared to other sources of variance such as heterogeneity in the tissue microstructure or the effects of CSF contamination or subject motion. Future studies will be needed to more fully explore the effects of signal noise on the measures of kurtosis anisotropy.

Since parameter mean and variability were analyzed in a small cohort of healthy subjects, it is unknown what the effect size of pathological changes will be on KFA and GFA relative to FA, and future studies will show whether or not the metric will turn out to have practical value in research or clinical work. However, one can imagine a situation where neurodegenerative changes could lead to a decrease in the number of crossing WM fiber bundles, resulting in a paradoxical increase in WM FA values but a decrease in WM KFA values on average (20).

It is of interest that KA_μ is typically very small in simulations (Figs. 1-3) and for in vivo experiments (Fig. 4), which is consistent with the results of Hansen et al. (15). This supports the use of W as an alternative to K for characterizing the overall kurtosis. This is of practical importance, since an efficient image acquisition protocol for W has recently been proposed (15). However, the fact that KA_μ is smaller than the other kurtosis anisotropy measures does not imply that it is necessarily less useful.

The ROIs plotted in Fig. 5 for human data are expected to contain different diffusion dynamics. In particular, the CC demonstrates the relationship between KFA, GFA, and FA in high anisotropy regions with largely well-defined fiber bundle orientations, whereas the SLF, CB, and CR represent WM regions with potentially more complex diffusion dynamics from interactions with other fiber bundles. For example, in Table 1, the SLF and CB have the highest average number of fiber bundle orientations detected of the WM ROIs, and KFA is significantly higher on average than FA, whereas the CC ROI has the lowest number of fiber bundles detected, and GFA and FA are higher on average than KFA.

The anisotropy described by the FA and KFA is sometimes referred to as “macroscopic” to indicate that it can be observed with conventional single pulsed diffusion MRI (31). By using double pulsed diffusion MRI, it is also possible to probe “microscopic anisotropy” to help better characterize complex diffusion dynamics, and several metrics for quantifying this have been proposed (32-35). While they are quite distinct from the kurtosis anisotropies investigated in this study, some measures of microscopic anisotropy are also closely related to the kurtosis tensor (33-35).

Conclusions

Diffusion anisotropy is an important aspect of tissue microstructure. However, anisotropy measures from the diffusion tensor, such as FA, can potentially take on small values despite significant diffusion anisotropy due to the presence of complex fiber bundle geometries. As a consequence, alternative measures of diffusion anisotropy, such as the KFA and GFA, may be of interest. KFA is based purely on the kurtosis tensor and is distinct from the conventional FA measure, as the kurtosis and diffusion tensors describe different features of the diffusing environment and can vary independently. It differs from other kurtosis anisotropy measures in depending only on the kurtosis tensor and in being defined in a manner more conceptually analogous to the original definition of the FA. GFA, on the other hand, uses the dODF to quantify the degree of preferential diffusion mobility and thereby effectively integrates information from both the diffusion and kurtosis tensors. By measuring higher order diffusion anisotropy, KFA and GFA can help to better characterize more complex diffusion profiles and may be particularly useful for regions where WM fiber bundles cross.

Appendix: Kurtosis Fractional Anisotropy for Two Identical Crossing Fibers

In order to better understand the physical meaning of the kurtosis fractional anisotropy, let us consider two identical crossing fiber bundles intersecting at an angle of 2θ . As in the simulation experiments of Fig. 2, we assume that both fiber bundles are non-exchanging,

cylindrically symmetric, Gaussian compartments, with the diffusion tensor eigenvalues $\lambda_{\parallel}$ $\lambda_{\perp}$. The fiber bundles both lie parallel to the xy -plane and are oriented at angles of $\pm\theta$ with respect to the x -axis. The diffusion tensor for the first fiber bundle (A) is

$$\mathbf{D}_A = \mathbf{R} \mathbf{D}_0 \mathbf{R}^T \quad [\text{A1}]$$

and the diffusion tensor for second bundle is

$$\mathbf{D}_B = \mathbf{R}^T \mathbf{D}_0 \mathbf{R}, \quad [\text{A2}]$$

where

$$\mathbf{D}_0 = \begin{bmatrix} \lambda_{\parallel} & 0 & 0 \\ 0 & \lambda_{\perp} & 0 \\ 0 & 0 & \lambda_{\perp} \end{bmatrix} \quad [\text{A3}]$$

and

$$\mathbf{R} = \begin{bmatrix} R_{11} & R_{12} & 0 \\ R_{21} & R_{22} & 0 \\ 0 & 0 & 1 \end{bmatrix} = \begin{bmatrix} \cos\theta & -\sin\theta & 0 \\ \sin\theta & \cos\theta & 0 \\ 0 & 0 & 1 \end{bmatrix} \quad [\text{A4}]$$

The matrix $\mathbf{R}$ rotates a vector in the xy -plane by an angle θ . As for all rotation matrices, $\mathbf{R}^{-1} = \mathbf{R}^T$

If the water fraction is f for bundle A and $(1-f)$ for bundle B, then the total diffusion tensor is

$$\mathbf{D} = f \mathbf{D}_A + (1-f) \mathbf{D}_B \quad [\text{A5}]$$

The components of the corresponding kurtosis tensor, $\mathbf{W}$, are given by

$$W_{ijkl} = \frac{1}{D^2} [f(D_{A,ij}D_{A,kl} + D_{A,ik}D_{A,jl} + D_{A,il}D_{A,jk}) + (1-f)(D_{B,ij}D_{B,kl} + D_{B,ik}D_{B,jl} + D_{B,il}D_{B,jk}) - D_{ij}D_{kl} - D_{ik}D_{jl} - D_{il}D_{jk}], \quad [\text{A6}]$$

where $D = \text{Tr}(\mathbf{D})/3$ is the mean diffusivity, $D_{A,ij}$ are the components of $\mathbf{D}_A$, and $D_{B,ij}$ are the components of $\mathbf{D}_B$. With the help of Eq. [A5], Eq. [A6] may be recast as

$$W_{ijkl} = \frac{f(1-f)}{D} [(D_{A,ij} - D_{B,ij})(D_{A,kl} - D_{B,kl}) + (D_{A,ik} - D_{B,ik})(D_{A,jl} - D_{B,jl}) + (D_{A,il} - D_{B,il})(D_{A,jk} - D_{B,jk})] \quad [\text{A7}]$$

Now consider the difference matrix

$$\delta \mathbf{D} \equiv \mathbf{D}_A - \mathbf{D}_B = \mathbf{R} \mathbf{D}_0 \mathbf{R}^T - \mathbf{R}^T \mathbf{D}_0 \mathbf{R}. \quad [\text{A8}]$$

This may be rewritten as

$$\delta \mathbf{D} = \mathbf{R}(\mathbf{D}_0 - \lambda_{\perp} \mathbf{I}) \mathbf{R}^T - \mathbf{R}^T(\mathbf{D}_0 - \lambda_{\perp} \mathbf{I}) \mathbf{R} = (\lambda_{\parallel} - \lambda_{\perp})(\mathbf{R} \mathbf{P} \mathbf{R}^T - \mathbf{R}^T \mathbf{P} \mathbf{R}), \quad [\text{A9}]$$

where $\mathbf{I}$ is the identity matrix and

$$\mathbf{P} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}. \quad [\text{A10}]$$

By using the fact that $R_{12} = -R_{21}$, a direct calculation then shows that

$$\delta \mathbf{D} = 2(\lambda_{\parallel} - \lambda_{\perp}) R_{11} R_{21} \mathbf{Q}, \quad [\text{A11}]$$

with

$$\mathbf{Q} \equiv \begin{bmatrix} 0 & 1 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}. \quad [\text{A12}]$$

From Eqs. [A4], [A7], [A8], and [A11], we then see that

$$W_{ijkl} = \frac{f(1-f)}{\overline{D}^2} (\lambda_{\parallel} - \lambda_{\perp})^2 \sin^2(2\theta) (Q_{ij} Q_{kl} + Q_{ik} Q_{jl} + Q_{il} Q_{jk}). \quad [\text{A13}]$$

Therefore, the parameters f , $\lambda_{\parallel}$, $\lambda_{\perp}$, and only θ affect the overall scaling of $\mathbf{W}$. Since the KFA is invariant with respect to this scaling factor, the KFA is strictly independent of f , $\lambda_{\parallel}$, $\lambda_{\perp}$, and θ . By applying the definition of the KFA, one may show that it always equals $\sqrt{13/15} \approx 0.931$.

For this same model, the FA, in contrast, depends significantly on all four adjustable parameters, illustrating the distinct information provided by the FA and KFA; the FA reflects the directional dependence of the diffusivity, while, for multiple Gaussian compartment models, the KFA reflects the directional dependence of the variance of the compartmental diffusivities.

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Abbreviations Used

DKI	Diffusional kurtosis imaging
DTI	diffusion tensor imaging
KA	kurtosis anisotropy
KFA	kurtosis fractional anisotropy
FA	fractional anisotropy
GFA	generalized fractional anisotropy
NFD	number of fiber directions
WM	white matter
dODF	diffusion orientation distribution function
CC	corpus callosum
CB	cingulum bundle

SLF	superior longitudinal fasciculus
CR	corona radiata
IC	internal capsule
EC	external capsule
LN	lenticular nucleus
Thal	thalamus

Fig. 1.

Multiple Gaussian compartment model for one WM fiber bundle orientation with only anisotropic diffusion (A) and an additional isotropic compartment (B). Numbers at the top of each column represent the ratio $\lambda_{\perp}/\lambda_{\parallel}$ for that column. The fiber bundle orientation depicts the orientation the diffusion ellipsoid for each of the separate compartments, where the colored ellipsoid represents simulated WM fiber bundles and the gray spheres represent simulated isotropic diffusion. The blue diffusion ellipsoid is taken from the net diffusion tensor and is a way of visualizing FA. The dODF is used to calculate GFA and is taken from Eq. [10], using the kurtosis dPDF representation (10). $W(n)$ illustrates the directional dependence of the kurtosis tensor and is calculated by Eq. [6]. The plots at the bottom of each column represent the anisotropy parameter values for $\lambda_{\perp}/\lambda_{\parallel}$ ratios between 0 and 1. Renderings of the diffusion ellipsoid, dODF, and $W(n)$ are not shown to scale to emphasize anisotropic features, as FA, KFA, or GFA are not affected by the overall scaling. In panel A, KA_{λ} and KA_{σ} are always zero, as discussed in the text.

Fig. 2. Multiple Gaussian compartment model for 2 crossing fibers with only anisotropic diffusion (A) and an additional isotropic compartment (B). Numbers at the top of each column represent the crossing angle for that column, and the 3D renderings depicted in Fig. 2 are calculated from the same equations as those in Fig. 1. The plots at the bottom of each column represent the anisotropy parameter values for simulated crossing angles for each integer value between 1 and 90 degrees.

Fig. 3. Multiple Gaussian compartment model for 3 crossing fibers with only anisotropic diffusion (A) and an additional isotropic compartment (B). Numbers at the top of each column represent the crossing angle for that column, and the 3D renderings depicted in Fig. 2 are calculated from the same equations as those in Fig. 1. The plots at the bottom of each column represent the anisotropy parameter values for simulated crossing angles for each integer value between 1 and 90 degrees. For this example, both FA and KA_μ drop to zero at 90 degrees, while all other measures are non-zero.

Fig. 4.

Representative anisotropy maps from a healthy volunteer. (A) Anisotropy maps for two slices taken from a healthy volunteer. MPRAGE and GFA color map (16) for the first slice (B) and second slice (C) point out a few regions of interest. (D) Sagittal MPRAGE image with white bars indicates the slice location for the parameter maps.

Fig. 5.

Anisotropy difference maps. Representative transverse (A) and (B), sagittal (C), and coronal (D) slices from the difference maps highlight differences in the anisotropy parameters. The first column illustrates the average of the normalized GFA colormaps (16) illustrating WM structures in the normalized data. The second column overlays the template ROIs on the mean GFA map. The ROIs shown are CC (red), CB (green), SLF (blue), CR and IC (yellow), EC (orange), other WM structures (magenta), Thal (light grey), and LN (dark grey). The anisotropy difference maps shown are indicated at the top of each column, and the NFD column shows the NFD map averaged across all subjects. There is a strong correlation between regions enhanced in the KFA-FA difference map and regions with multiple fiber bundle orientations detected, depicted in the NFD maps.

Fig. 6. Representative transverse, sagittal, and coronal slices from the ICBM WM template as well as the mean of the normalized FA, GFA, and KFA parameter maps across all 5 subjects.

Fig. 7.

(A) Inter- and (B) Intra-subject variability maps for FA, GFA, and KFA for the same slices depicted in Fig. 6. Inter-subject variability is calculated as the voxel-wise coefficient of variation of the parameter across all 5 subjects. Intra-subject variability is calculated as the voxel-wise coefficient of variation of the parameter for each of the 3 independent DKI acquisitions from each subject, which is then averaged across all 5 subjects. Inter-subject variability is comparable for each of the three parameters, although GFA inter-subject variability is slightly lower. However, intra-subject variability is higher for KFA than for FA or GFA, which may reflect the lower relative precision for the kurtosis tensor compared to the diffusion tensor.

Table 1**Mean parameter values within each region of interest (ROI)**

	WM	CC	CB	CR	SLF	Thal	LN
FA	0.412 (0.131)	0.494 (0.144)	0.313 (0.100)	0.390 (0.087)	0.377 (0.093)	0.274 (0.054)	0.200 (0.086)
GFA	0.539 (0.151)	0.626 (0.156)	0.446 (0.140)	0.527 (0.101)	0.517 (0.124)	0.366 (0.070)	0.275 (0.108)
KFA	0.439 (0.115)	0.469 (0.124)	0.466 (0.121)	0.441 (0.072)	0.455 (0.115)	0.338 (0.048)	0.365 (0.072)
NFD	1.325 (0.337)	1.242 (0.290)	1.622 (0.239)	1.485 (0.407)	1.658 (0.330)	1.343 (0.245)	1.561 (0.337)

Values represent the mean ($\pm$ standard deviation) for the anisotropy measures in each ROI pooled from the average scans of all five subjects after normalization to the ICBM WM template. The mean parameter maps are shown in Figure 6.

CB, cingulum bundle; CC, corpus callosum; CR, corona radiata; FA, fractional anisotropy; GFA, generalized fractional anisotropy; KFA, kurtosis fractional anisotropy; LN, lenticular nucleus; NFD, number of fiber directions; SLF, superior longitudinal fasciculus; Thal, thalamus; WM, white matter.

Table 2

Inter-subject variability within each region of interest (ROI)

	WM	CC	CB	CR	SLF	Thal	LN
FA	0.155(0.094)	0.151(0.083)	0.290(0.130)	0.127(0.072)	0.198(0.122)	0.107(0.042)	0.185(0.075)
GFA	0.138(0.091)	0.130(0.080)	0.259(0.124)	0.109(0.069)	0.180(0.120)	0.100(0.039)	0.168(0.072)
KFA	0.153(0.085)	0.161(0.082)	0.202(0.092)	0.105(0.059)	0.146(0.091)	0.155(0.073)	0.222(0.080)

Values represent the mean ($\pm$ standard deviation) of the inter-subject variability of the anisotropy measures in each ROI. The inter-subject variability map was calculated as the voxel-wise coefficient of variation between all five subjects after normalization to the ICBM WM template. The inter-subject variability map is shown in Figure 7A.

CB, cingulum bundle; CC, corpus callosum; CR, corona radiata; FA, fractional anisotropy; GFA, generalized fractional anisotropy; KFA, kurtosis fractional anisotropy; LN, lenticular nucleus; SLF, superior longitudinal fasciculus; Thal, thalamus; WM, white matter.

Table 3

Intra-subject variability within each region of interest (ROI)

	WM	CC	CB	CR	SLF	Thal	LN
FA	0.068(0.031)	0.075(0.032)	0.109(0.028)	0.049(0.019)	0.066(0.026)	0.069(0.019)	0.110(0.036)
GFA	0.059(0.030)	0.062(0.031)	0.091(0.027)	0.043(0.018)	0.059(0.026)	0.066(0.018)	0.097(0.033)
KFA	0.111(0.048)	0.114(0.046)	0.128(0.052)	0.085(0.033)	0.104(0.045)	0.138(0.044)	0.140(0.035)

Values represent the mean ($\pm$ standard deviation) of the intra-subject variability of the anisotropy measures in each ROI pooled from all five subjects. Intra-subject variability maps were calculated as the voxel-wise coefficient of variation between the three independent scans of each subject after normalization to the ICBM WM template. The mean intra-subject variability map is shown in Figure 7B.

CB, cingulum bundle; CC, corpus callosum; CR, corona radiata; FA, fractional anisotropy; GFA, generalized fractional anisotropy; KFA, kurtosis fractional anisotropy; LN, lenticular nucleus; SLF, superior longitudinal fasciculus; Thal, thalamus; WM, white matter.