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Towards better MR characterization of neural tissues using directional diffusion kurtosis analysis

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MR diffusion kurtosis imaging (DKI) was proposed recently to study the deviation of water diffusion from Gaussian distribution. Mean kurtosis, the directionally averaged kurtosis, has been shown to be useful in assessing pathophysiological changes, thus yielding another dimension of information to characterize water diffusion in biological tissues. In this study, orthogonal transformation of the 4th order diffusion kurtosis tensor was introduced to compute the diffusion kurtoses along the three eigenvector directions of the 2nd order diffusion tensor. Such axial ($K_{//}$) and radial ($K_{\perp}$) kurtoses measured the kurtoses along the directions parallel and perpendicular, respectively, to the principal diffusion direction. DKI experiments were performed in normal adult ($N=7$) and formalin-fixed rat brains ($N=5$). DKI estimates were documented for various white matter (WM) and gray matter (GM) tissues, and compared with the conventional diffusion tensor estimates. The results showed that kurtosis estimates revealed different information for tissue characterization. For example, $K_{//}$ and $K_{\perp}$ under formalin fixation condition exhibited large and moderate increases in WM while they showed little change in GM despite the overall dramatic decrease of axial and radial diffusivities in both WM and GM. These findings indicate that directional kurtosis analysis can provide additional microstructural information in characterizing neural tissues.

Keywords: Water diffusion; Diffusion kurtosis; Directional kurtosis; Diffusion kurtosis tensor; DKI; Non-Gaussian diffusion; Restricted diffusion; Orthogonal transformation

Introduction

Diffusion kurtosis imaging (DKI) was recently proposed to characterize the non-Gaussian water diffusion behavior in neural tissues (Fieremans et al., 2008; Jensen et al., 2005; Lu et al., 2006). Biological tissues are heterogeneous in nature comprising multiple compartments (Le Bihan, 1991). Thus the Gaussian distribution generally assumed for free or unrestricted water diffusion is insufficient to describe the diffusion process in biological environment (Karger, 1985). In addition, the dependency of diffusion-weighted (DW) signal on *b*-value has been observed to be non-monoexponential in neural tissues (Basser and Jones, 2002; Mulkern et al., 1999; Niendorf et al., 1996). To characterize such non-Gaussian diffusion behavior, kurtosis, the 4th central moment of the diffusion distribution (Balanda and Macgillivray, 1988), was introduced (Jensen et al., 2005). It is a dimensionless measure that can be either positive or negative. Positive kurtosis means that distribution is more sharply peaked than Gaussian. The higher the diffusion kurtosis, the more the water molecule diffusion deviates from Gaussian distribution, indicative of a more restricted diffusion environment. Apparent diffusion kurtosis has been estimated by acquiring DW signals at multiple *b*-values up to a maximum of 2500 s/mm^2 in humans (Jensen et al., 2005; Lu et al., 2006). Because the 4th order diffusion kurtosis tensor (KT) is fully symmetric and has 15 independent components, DKI experiments are typically performed in more than 15 directions to obtain the full KT.

Several approaches have been proposed to study the non-monoexponential diffusion behavior. They include the multi-compartment model (Clark et al., 2002), statistical diffusion model (Yablonskiy et al., 2003), generalized diffusion tensors (Liu et al., 2004; Ozarslan and Mareci, 2003) and q-space imaging (Callaghan, 1991). Among them, q-space imaging, in which water diffusion displacement probability profile is estimated, is deemed to provide a robust characterization of the diffusion related structural changes in diseased neural tissues (Assaf et al., 2005, 2003; Biton et al., 2006; Nossin-Manor et al., 2007). Despite of the advantage of quantitatively measuring the water displacement, q-space imaging often requires a long scan time, large *b*-values and a strong gradient. The DKI approach largely circumvents these limitations, offering a more practical means to investigate the non-Gaussian diffusion behavior with relative ease and reasonable speed. It utilizes the non-monoexponential dependence of DW signals on *b*-values to map the diffusion kurtosis as a biomarker for microstructural changes in various neural tissues, including both white and gray matters.

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Recent experimental findings in human DKI studies were promising (Falangola et al., 2007a,b; Helpern et al., 2007; Jensen et al., 2005; Lu et al., 2006; Ramani et al., 2007). Mean kurtosis (*MK*), the average apparent kurtosis along all diffusion gradient encoding directions, was measured and demonstrated to offer an improved sensitivity in detecting developmental and pathological changes in neural tissues as compared to the conventional diffusion tensor imaging (DTI). One might argue that by simply taking the mean of the apparent kurtoses measured along all diffusion directions it would reduce the sensitivity and specificity in probing diffusion kurtosis change occurring along a specific direction, for instance, parallel or perpendicular to the principal diffusion eigenvector as denoted as axial or radial direction, respectively. Given that axial and radial diffusivity analyses have been successfully employed in numerous studies to elucidate the specific neural tissue pathologies in animal models (Song et al., 2003, 2002; Sun et al., 2006) and humans (Trip et al., 2006), it is valuable to analyze the directional kurtoses by obtaining the water diffusion kurtoses along these two directions. Such directional diffusion kurtosis analysis may provide unique and complementary information regarding the biological systems, thus improving the MR diffusion characterization of neural tissues in normal, developmental or pathological states.

In this study, an orthogonal transformation of the 4th order KT was proposed to compute the diffusion kurtoses along the directions of the three diffusion eigenvectors. Histological fixation is known to alter the cellular structure and hence the restriction to water diffusion (Does et al., 2003; Schwartz et al., 2005; Takahashi et al., 2002; Thelwall et al., 2006; Yong-Hing et al., 2005), likely leading to varying extents of water diffusion restriction along the axial and radial directions. Therefore, DKI experiments were performed in both normal and formalin-fixed adult rat brains to document both DKI and DTI estimates in various brain tissues, and to evaluate whether directional kurtosis analysis improves tissue characterization.

Materials and methods

Theory

In conventional DTI, the 2nd order diffusion tensor (DT) is fully characterized by its eigenvalues (λ_i with i=1, 2 3 and $\lambda_1>\lambda_2>\lambda_3$) and the corresponding orthonormal eigenvectors that can be obtained by matrix diagonalization (Basser et al., 1994). In DKI (Jensen et al., 2005; Lu et al., 2006), both apparent diffusion coefficient (D_{app}) and apparent diffusion kurtosis (K_{app}) along each applied diffusion gradient direction are estimated together by fitting the following equation with the multiple DW signals acquired using a range of b-values:

$$\ln[S(b)/S(0)] \approx -bD_{\text{app}} + \frac{1}{6}b^2 D_{\text{app}}^2 K_{\text{app}}, \tag{1}$$

where $S(b)$ is the DW signal intensity at a particular b-value, and $S(0)$ the signal without applying any diffusion gradient. To obtain reliable curve fitting, a sufficient b-value range must be chosen to permit as much non-monoexponential decay as possible. It is noteworthy that the kurtosis formulation above is valid only for a limited b-value range because the quadratic term $-bD_{\text{app}} + \frac{1}{6}b^2 D_{\text{app}}^2 K_{\text{app}}$ will increase with b-value after the minima. Therefore, b-values chosen to fit Eq. (1) should be smaller than $b_{\text{minima}} = 3/(D_{\text{app}} K_{\text{app}})$.

The mean kurtosis (*MK*) is measured as:

$$MK = \frac{1}{n}\sum_{i=1}^{n} (K_{\text{app}})_i, \tag{2}$$

where $(K_{\text{app}})_i$ is the K_{app} along i^{th} direction and n is the total number of directions in which diffusion measurements are carried out. K_{app} at a particular direction is related to a 4th order kurtosis tensor (*KT*) by:

$$K_{\text{app}} = \frac{MD^2}{D_{\text{app}}^2} \cdot \sum_{i=1}^{3}\sum_{j=1}^{3}\sum_{k=1}^{3}\sum_{l=1}^{3} n_i n_j n_k n_l W_{ijkl}, \tag{3}$$

where mean diffusivity is $MD = \frac{1}{3}\sum_{i=1}^{3}\lambda_i$, n_i the component of the diffusion encoding gradient unit vector and W_{ijkl} the individual element of *KT*. Note that *KT* has 15 independent elements only due to the symmetry of different diffusion processes probed by MR. Because of the mathematical complexity of the 4th order tensor (Qi, 2005), individual *KT* elements, eigenvalues and eigenvectors are yet to be explored in terms of their direct physical relevance to the diffusion processes. Nevertheless, KT can be transformed from the standard Cartesian coordinate system to another coordinate system in which the 3 orthonormal eigenvectors of DT are the base coordinate vectors by (Qi et al., in press):

$$\hat{W}_{ijkl} = \sum_{i'=1}^{3}\sum_{j'=1}^{3}\sum_{k'=1}^{3}\sum_{l'=1}^{3} e_{ii'} e_{jj'} e_{kk'} e_{ll'} W_{i'j'k'l'}. \tag{4}$$

From Eqs. (3) and (4), the kurtosis along the individual DT eigenvector is:

$$K_i = \frac{MD^2}{\lambda_i^2} \cdot \hat{W}_{iiii}. \tag{5}$$

Thus the axial ($K_{//}$) and radial kurtosis ($K\perp$) can be obtained from the three newly derived kurtoses:

$$K_{//} = K_1 \tag{6}$$

$$K_{\perp} = \frac{K_2 + K_3}{2}. \tag{7}$$

Note that these two directional kurtoses are not related to *MK* by simple linear combination, i.e., $MK \neq (K_{//} + 2K\perp)/3$, because the 3D distribution of the 4th order kurtosis tensor cannot be simply represented as an ellipsoid. In conventional DTI, however, *MD* is related directly to the axial diffusivity ($\lambda_{//}$) and radial diffusivity ($\lambda\perp$) by $MD = (\lambda_{//} + 2\lambda\perp)/3$ owing to the nature of 2nd order diffusion tensor where three eigenvalues represent the diffusion coefficients along three orthogonal eigenvectors. To examine the anisotropy of these directional kurtoses, the fractional anisotropy of kurtosis (FA_K) can also be conveniently defined in a way similar to that in DTI (Basser and Pierpaoli, 1996) as:

$$FA_K = \sqrt{\frac{3}{2} \cdot \frac{(K_1 - \overline{K})^2 + (K_2 - \overline{K})^2 + (K_3 - \overline{K})^2}{K_1^2 + K_2^2 + K_3^2}}, \tag{8}$$

where $\overline{K} = \frac{1}{3}\sum_{i=1}^{3} K_i$.