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Preliminary evaluation of accelerated microscopic diffusional kurtosis imaging (μ DKI) in a rodent model of epilepsy

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Abstract

Purpose: Our study aimed to develop accelerated microscopic diffusional kurtosis imaging (μ DKI) and preliminarily evaluated it in a rodent model of chronic epilepsy.

Methods: We investigated two μ DKI acceleration schemes of reduced sampling density and angular range in a phantom and wild-type rats, and further tested μ DKI method in pilocarpine-induced epilepsy rats using a 4.7 Tesla MRI. Single slice average μD_{app} and μK_{app} maps were derived, and Nissl staining was obtained.

Results: The kurtosis maps from two accelerated μ DKI sampling schemes (sampling density and range) are very similar to that using fully sampled data (SSIM>0.95). For the epileptic models, μ DKI showed noticeably different contrast from those obtained with conventional DKI. Specifically, the average μK_{app} was significantly less than that of the average of K_{app} (0.15 ± 0.01 vs. 0.47 ± 0.02) in the ventricle.

Conclusions: Our study demonstrated the feasibility of accelerated in vivo μ DKI. Our work revealed that μ DKI provides complementary information to conventional DKI method, suggesting that advanced DKI sequences are promising to elucidate tissue microstructure in neurological diseases.

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Introduction

Diffusional kurtosis imaging (DKI) measures the degree of non-Gaussian diffusion and has been increasingly used for neuroimaging [1, 2]. DKI reveals sub-voxel tissue heterogeneity and complexity in central nervous system disorders including epilepsy, Alzheimer's disease (AD) and stroke [3–7]. For example, DKI refines the heterogeneous diffusion-weighted imaging (DWI) lesion that is associated with graded metabolic derangement, which can be used for enhanced characterization of ischemic tissue injury [8–10]. It's helpful to point that routine DKI is based on single diffusion encoding (SDE), a pair of pulsed gradients that encode the diffusional displacement. Recently, double diffusion encoding (DDE) MRI has shown promise to extract important information that could not be easily inferred from the SDE experiments [10–17]. For instance, angular DDE can quantify microscopic properties affecting the spin's diffusion, including estimation of cell size [18, 19], pore diameter [20], and microscopic anisotropy [16, 21–23].

The routine kurtosis measurement can arise from both restricted diffusion and diffusional heterogeneity [1, 24]. Recently, microscopic diffusional kurtosis imaging (μ DKI) based on symmetrized DDE (s-DDE) echo planar imaging (EPI) has been demonstrated by Ji et al. [25]. In vivo μ DKI displayed some unique image features that complement conventional DKI. However, the initial μ DKI scan required diffusion sampling along a large number of directions, resulting in a prolonged acquisition time. Efficient μ DKI acquisition and processing schemes are necessary in order to expedite its translation to the routine in vivo applications. The current work aimed to shorten the scan time of μ DKI by reducing the sampling density and range of the modulation angle. Of note, cerebral atrophy is associated with epilepsy, resulting in noticeable diffusional heterogeneity [26–28]. As a result, we preliminarily tested μ DKI in a rodent model of chronic epilepsy and evaluated its potential diagnostic value.

Material and methods

2.1 Phantom

The μ DKI was tested using a three-compartment phantom. The left centrifugal tube comprised 40% sucrose mixed with 1% agarose and 1% agarose alone, representing two superimposed Gaussian diffusion pools. The right centrifugal tube comprised 20 μ m monosphere acrylic beads (MX-2000, Esprix Technologies, Sarasota, FL) mixed with 1% agarose. The third compartment (the space between two centrifugal tubes) was filled with 1% agarose gel.

2.2 Animal model of temporal lobe epilepsy

In vivo experiments have been approved by the local Institutional Animal Care and Use Committee. Adult male Sprague-Dawley (Harlan/Envigo, Indianapolis, IN) were divided into a control group (n=5) and a lithium-pilocarpine-induced chronic epilepsy group (n=5) [29, 30]. Briefly, rats were injected intraperitoneally with 3 mmol/kg lithium chloride, followed by 1 mg/kg methylscopolamine subcutaneously after thirteen hours. The subcutaneous injection was repeated with 30 mg/kg pilocarpine thirty minutes later to

trigger status epilepticus within 10–30 minutes. Status epilepticus was defined as continuous behavioral seizure activity scored as stage 4 or 5 according to the Racine score and lasting at least 90 minutes [31]. Diazepam (10 mg/kg, i.p.) was administered after 1 hour of status epilepticus to terminate seizures. Repeated diazepam (5 mg/kg) was injected unless status epilepticus was terminated. Two weeks after status epilepticus, rats were video recorded (8 hours/day, 5 days per week) for monitoring chronic spontaneous recurrent seizures. The chronic epilepsy model was considered successful when three or more spontaneous recurrent seizures were observed. For the control group, lithium preconditioning was followed by saline administration instead of pilocarpine. Rats were anesthetized with 1.5–2.0% isoflurane air during the MRI experiment. Respiratory rate and body temperature were monitored online (SA Instruments, Stony Brook, NY), and the temperature was maintained by a circulating warm water jacket positioned around the torso (Stryker Temperature Therapy Pad, Kalamazoo, MI).

2.3 MRI

MRI scans were performed using a 4.7 T small-bore Biospec MRI (Bruker, Billerica, MA) with a dual radiofrequency (RF) coil setup. For the phantom scan, μ DKI was acquired with 4 b-values (0, 1000, 1500 and 2500 s/mm²), 26 angles evenly spanning from 0 to 360° in the x-y plane (NAE = 4 and scan time = 11 min), field of view (FOV) of 50×50 mm² and 8 mm slice thickness (Matrix size= 64×64, repetition time (TR)/echo time (TE) = 3000/76 ms). For in vivo scans, we performed DKI using both tensor-based DKI and μ DKI methods (FOV= 20×20 mm², Matrix = 64×64, slice thickness = 2 mm). For the standard DKI protocol, diffusion images (1000 and 2500 s/mm²) were acquired along 30 diffusion directions in addition to a single reference image of b=0 (δ/γ = 4/17.5 ms, TR/TE = 3000/75.8ms, NAE = 4, and scan time = 10 min 50 s) [32]. μ DKI was acquired with 3 b-values (1000 and 2500 s/mm²), 26 angles evenly spanning from 0 to 360° through x-y, x-z and y-z planes, respectively, in addition to a single reference image of b=0 (NAE = 8, TR/TE = 3000/75.8 ms, and scan time = 66 min). T₂-weighted EPI images were obtained with two TE of 30 and 100 ms (TR=3250 ms, NAE=16). Moreover, a high-resolution rapid acquisition with relaxation enhancement (RARE) image was performed (FOV= 20×20 mm², Matrix = 128×128, TE=35 ms).

2.4 Data Processing

Images were processed in MATLAB (Mathworks, Natick, MA). Conventional DKI was analyzed using established routines [33, 34]. For μ DKI, the diffusion-induced signal can be formulated as,

$$\ln\left\{\frac{E(q, \phi)}{E_0}\right\} = E_{c,0} + E_{c,2}\cos(2\phi) + E_{c,4}\cos(4\phi) + \dots + E_{s,2}\sin(2\phi) + \dots \quad (1)$$

where $E_{c,\tilde{n}}$ and $E_{s,\tilde{n}}$ are amplitudes of nth-cycle cosine and sine terms of the natural logarithm of the μ DKI signal with respect to ϕ . We investigated three sampling schemes of ϕ : 1) [0°, 360°] with intervals of 13.8°. 2) [0°, 360°] with intervals of 27.7°, and 3) [0, 180°] with intervals of 13.8°. The diffusion and kurtosis terms were calculated according to,

$$D = \frac{E_{c,\tilde{0}} - 3E_{c,\tilde{4}}}{-b} \quad (2.a)$$

$$K = \frac{4!E_{c,\tilde{4}}}{\left(E_{c,\tilde{0}} - 3E_{c,\tilde{4}}\right)^2} \quad (2.b)$$

The in vivo μ DKI was repeated along x-y, x-z, and y-z planes, and the diffusion and kurtosis metrics were denoted as average apparent μ D (average μD_{app}) and average apparent μ K (average μK_{app}), respectively. In addition, the diffusional kurtosis tensor W_{ijkl} was calculated from the tensor-based DKI approach, which was used to calculate apparent diffusion (D_{app}) and apparent kurtosis (K_{app}). To compare with μ DKI, the average D_{app} and K_{app} along x-y, x-z, and y-z planes are calculated and denoted as average apparent diffusion (average D_{app}) and average apparent kurtosis (average K_{app}), respectively.

We calculated structural similarity (SSIM) index to assess the accuracy of accelerated μ DKI schemes. Diffusion and kurtosis from three representative regions of interests (ROIs) of white matter (WM), gray matter (GM), and ventricle were reported as their mean $\pm$ standard deviation (SD). We compared the diffusion and kurtosis indexes from conventional DKI and μ DKI using two-tailed paired Student's t-test in control and epilepsy groups. Indices from the same ROIs were also compared using two-tailed unpaired Student's t-test between control and epilepsy groups. In addition, the false discovery rate (FDR, $n=6$) correction was performed for statistical analysis. P values less than 0.05 were considered statistically significant.

2.5 Histology

Animals were euthanized after MRI, followed by transcatheter perfusion with PBS and exsanguination. Brains were dissected and frozen in 2-methylbutane on dry ice at -35°C . Coronal cryosections were collected every 30 μm throughout the entire brain and the standard Nissl staining was performed.

Results

Figure 1A shows the μ DKI pulse sequence. Two pairs of diffusion gradients ($\mathbf{g}_1$ and $\mathbf{g}_2$) were applied consecutively with their relative magnitude modulated by trigonometric functions of ϕ . The echo time (TE) in μ DKI sequence can be expressed as $TE = TE' + TE'' + \dots$. In vivo μ DKI was repeated with gradients along x-y, x-z and y-z plane (Fig. 1B), in which the angle ϕ spans from 0 to 360° , uniformly with intervals of 13.8° in each plane.

The accelerated μ DKI schemes were first evaluated using a triple compartment phantom (Figure 2A). Figure 2B shows the diffusion and kurtosis maps from different sampling schemes. The original μ DKI approach with denoted as $(0, 360^\circ)_{26}$ with ϕ from 0 to 360° in 26 steps. The second scheme halved the sampling density from 26 to 13 (i.e., $(0, 360^\circ)_{13}$)

and the third scheme reduced ϕ from 0 to 360° to 0 to 180° (i.e., $(0, 180^\circ)_{13}$). The kurtosis from the left ROI (mixed Gaussian compartment) was nearly zero from all three schemes. The kurtosis from the right ROI (monosphere beads gel compartment) showed little difference among the three approaches (0.42 ± 0.03 , 0.42 ± 0.03 and 0.41 ± 0.03), with their SNR being 16.5, 13.7 and 15.2, respectively.

We then evaluated μ DKI in normal rats. Figure 3A shows signals from WM and GM as a function of ϕ for diffusion b value of 1000 and 2500 s/mm² from a representative normal rat. The signal displays a prominent 4ϕ oscillation pattern for both WM and GM. The amplitude of oscillation in WM is larger than that in GM, consistent with the fact that diffusion in WM is more restricted than that of GM [35]. Figure 3B shows the diffusion and kurtosis maps from conventional DKI and three μ DKI approaches ($(0, 360^\circ)_{26}$, $(0, 360^\circ)_{13}$ and $(0, 180^\circ)_{13}$). μ DKI appears to provide higher contrast between corpus callosum and cortex, consistent with that observed in Ji et al. [25]. To compare the accelerated μ DKI images, we calculated SSIM between kurtosis images derived from the two accelerated μ DKI schemes with respect to that using the fully sampled μ DKI data, being 0.96 ± 0.04 and 0.97 ± 0.05 , respectively. This shows that accelerated μ DKI schemes provide nearly identical images as the fully sampled μ DKI approach.

Figure 4A shows μ DKI from a representative chronic epilepsy rat brain. The average D_{app} map from conventional DKI and the average μD_{app} map from μ DKI are in good agreement with each other. In contrast, the average μK_{app} map displayed a different pattern from that of the average K_{app} map, particularly in the ventricle. Figure 4B shows T₂-weighted RARE image and Nissl staining from control and epileptic rats. The epileptic brain had noticeable atrophy with enlarged ventricles, consistent with the chronic epilepsy model [28]. Diffusion and kurtosis values in WM, GM, and ventricle from the control and epilepsy groups were listed in Table 1. Of importance, the average μK_{app} is significantly lower than average K_{app} in CSF from the epilepsy group (0.15 ± 0.01 vs 0.47 ± 0.02 , $P < 0.05$). In addition, the average μK_{app} of WM is significantly higher in the epilepsy group than that in control group (0.75 ± 0.02 vs 0.69 ± 0.04 , $P < 0.05$) while the average K_{app} did not show a significant difference.

Discussion

μ DKI is a relatively new diffusion MRI methodology that isolates compartmental kurtosis from diffusional heterogeneity. Establishment of expedited μ DKI acquisition scheme is needed before it can be translated to routine preclinical and clinical applications. Our study evaluated two μ DKI sampling schemes to reduce its acquisition time and validated them both in phantom and in vivo. The μ DKI approach employs two pairs of gradients modulated as a function of ϕ , which needs to span a range of at least 180° with a 2-cycle modulation, per the Nyquist criterion. Indeed, our results confirmed that the acquisition time can be noticeably shortened while providing satisfactory images (SSIM > 0.95), promising for in vivo applications.

Interestingly, the μ DKI shows a noticeable difference from conventional DKI in the animal model of chronic epilepsy. μK_{app} displays enlarged ventricle, consistent with cerebral

atrophy in the model [27]. The average K_{app} in the ventricle is significantly higher than μK_{app} . The inflated ventricular average K_{app} is likely due to partial volume effect and/or diffusional heterogeneity. It's worth mentioning that μK_{app} was significantly different between epilepsy and control groups in WM, which is likely attributable to chronic epilepsy-induced structural changes. Indeed, it has shown that patients with temporal lobe epilepsy have diffusion abnormalities in WM [36, 37]. Histopathological examinations documented disruption of myelin sheaths and altered axonal density [38]. Our results suggest that μDKI is promising to complement routine DKI for detection of microstructural changes following epilepsy.

Our study has a few limitations. First, we used a single slice μDKI pulse sequence for in vivo application. Although the μDKI pulse sequence can be extended for multi-slice readout due to the separation of s-DDE preparation and fast EPI readout, the inter-slice relaxation recovery needs to be properly accounted for. This may require correction based on relaxation measurement that is beyond the scope of our current work. Second, the s-DDE preparation was repeated in x-y, x-z, and y-z planes to estimate the average μD_{app} and μK_{app} metrics in vivo. Such an approach, strictly speaking, may not be rotationally invariant. Nevertheless, μDKI provides a reasonable estimation of tissue diffusion and kurtosis images that are clearly different from conventional DKI. Further evaluation of its diagnostic value is needed to investigate μDKI in a host of disorders including epilepsy and acute stroke.

Conclusion

Our study investigated accelerated μDKI acquisition and processing approaches and preliminarily demonstrated its utility in a rodent model of chronic epilepsy. The results suggest that advanced DKI complements routine diffusion MRI for improved characterization of tissue microstructure changes in neurological disorders such as epilepsy.

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Figure 1:

The diagrams of the μ DKI pulse sequence. **A)** Two pairs of diffusion gradients ($\mathbf{g}_1$ and $\mathbf{g}_2$) are orthogonal to one another, with their magnitudes modulated by the trigonometry of angle ϕ . **B)** The μ DKI diffusion sampling scheme used in our study. The arrows indicate the directions of the 78 independent vectors $\vec{q} = \gamma g \delta (g \cdot \cos(\phi) \vec{e}_1 + g \cdot \sin(\phi) \vec{e}_2)$, which are uniformly distributed in x-y, x-z, and y-z planes.

Figure 2:

Phantom validation of the expedited μDKI. **A)** A schematic illustration of the triple-compartment diffusion phantom. **B)** Diffusion and kurtosis maps obtained from three sampling schemes of μDKI, 0 to 360° with 26 steps (i.e., $(0-360^\circ)_{26}$), 0 to 360° with 13 steps (i.e., $(0-360^\circ)_{13}$) and 0 to 180° with 13 steps (i.e., $(0-180^\circ)_{13}$).

Figure 3:

Demonstration of μ DKI from a representative normal rat. **A)** The normalized and natural logarithmic μ DKI signals as a function of ϕ . **B)** Average D_{app} and K_{app} maps obtained from conventional DKI, average μD_{app} and μK_{app} maps obtained from three sampling schemes of μ DKI, 0 to 360° with 26 steps (i.e., $(0-360^\circ)_{26}$), 0 to 360° with 13 steps (i.e., $(0-360^\circ)_{13}$) and 0 to 180° with 13 steps (i.e., $(0-180^\circ)_{13}$).

Figure 4:

Demonstration of μ DKI from a representative chronic epilepsy rat. **A)** Comparison of diffusion and kurtosis images from the conventional DKI (average D_{app} and K_{app}) and μ DKI (average μD_{app} and μK_{app}). **B)** T₂-weighted RARE image and the Nissl-staining from control and chronic epileptic rats.

Table 1.

Comparison of in vivo conventional DKI and μ DKI measurements in white matter (WM), gray matter (GM) and ventricle of wild-type and epilepsy rat brains (Mean $\pm$ SD). Paired t-tests were performed in control and epilepsy groups, and unpaired t-tests were performed between control and epilepsy group. A false discovery rate (FDR, $n=6$) correction was performed. Letters in superscript (e.g., a, b) indicate the statistically significant difference between metrics.

		Control	Epilepsy
Average D_{app} ($\mu m^2/ms$)	WM	0.81 $\pm$ 0.03	0.78 $\pm$ 0.04
	GM	0.80 $\pm$ 0.04	0.82 $\pm$ 0.05
	CSF	1.89 $\pm$ 0.11 ^{ae}	2.81 $\pm$ 0.22 ^e
Average K_{app}	WM	0.73 $\pm$ 0.06 ^b	0.76 $\pm$ 0.02
	GM	0.55 $\pm$ 0.05	0.54 $\pm$ 0.03
	CSF	0.63 $\pm$ 0.09 ^{cf}	0.47 $\pm$ 0.02 ^{df}
Average μD_{app} ($\mu m^2/ms$)	WM	0.80 $\pm$ 0.03	0.78 $\pm$ 0.03
	GM	0.82 $\pm$ 0.04	0.83 $\pm$ 0.03
	CSF	2.08 $\pm$ 0.14 ^{ag}	2.82 $\pm$ 0.12 ^g
Average μK_{app}	WM	0.69 $\pm$ 0.04 ^{bh}	0.75 $\pm$ 0.02 ^h
	GM	0.53 $\pm$ 0.04	0.55 $\pm$ 0.02
	CSF	0.27 $\pm$ 0.09 ^{ci}	0.15 $\pm$ 0.01 ^{di}

^aSignificant difference between average D_{app} and average μD_{app} of CSF in the control group ($p<0.05$).

^bSignificant difference between average K_{app} and average μK_{app} of WM in the control group ($p<0.05$).

^cSignificant difference between average K_{app} and average μK_{app} of CSF in the control group ($p<0.05$).

^dSignificant difference between average K_{app} and average μK_{app} of CSF in epilepsy rat group ($p<0.05$).

^eSignificant difference of average D_{app} of CSF between control and epilepsy rat group ($p<0.05$).

^fSignificant difference of average K_{app} of CSF between control and epilepsy rat group ($p<0.05$).

^gSignificant difference of average μD_{app} of CSF between control and epilepsy rat group ($p<0.05$).

^hSignificant difference of average μK_{app} of WM between control and epilepsy rat group ($p<0.05$).

ⁱSignificant difference of average μK_{app} of CSF between control and epilepsy rat group ($p<0.05$).