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Validation of fast diffusion kurtosis MRI for imaging acute ischemia in a rodent model of stroke

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Abstract

Diffusion-weighted imaging (DWI) captures ischemic tissue that is likely to infarct, and has become one of the most widely used acute stroke imaging techniques. Diffusion kurtosis imaging (DKI) has lately been postulated as a complementary MRI method to stratify the heterogeneously damaged DWI lesion. However, the conventional DKI acquisition time is relatively long, limiting its use in the acute stroke setting. Recently, Hansen et al. proposed a fast kurtosis mapping method and demonstrated it in fixed brains and control subjects. The fast DKI approach provides mean diffusion and kurtosis measurements under substantially reduced scan time, making it amenable to acute stroke imaging. Because it is not practical to obtain and compare different means of DKI to test whether the fast DKI method can reliably detect diffusion and kurtosis lesions in acute stroke patients, our study investigated its diagnostic value using an animal model of acute stroke, a critical step before fast DKI acquisition can be routinely applied in the acute stroke setting. We found significant correlation, per voxel, between the diffusion and kurtosis coefficients measured using the fast and conventional DKI protocols. In acute stroke rats, both DKI methods yielded diffusion and kurtosis lesions that were in good agreement. Importantly, substantial kurtosis/diffusion lesion mismatch was observed using the conventional ($26 \pm 13\%$, $P < 0.01$) and fast DKI methods ($23 \pm 8\%$, $P < 0.01$). In addition, regression analysis showed that the kurtosis/diffusion lesion mismatch obtained using conventional and fast DKI methods were substantially correlated ($R^2 = 0.57$, $P = 0.02$). Our results confirmed that the recently proposed fast DKI method is capable of capturing heterogeneous diffusion and kurtosis lesions in acute ischemic stroke, and thus is suitable for translational applications in the acute stroke clinical setting.

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Keywords

acute stroke; diffusion weighted imaging (DWI); diffusion kurtosis imaging (DKI); mean diffusion (MD); mean kurtosis (MK)

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1. INTRODUCTION

Diffusion-weighted imaging (DWI), which captures acute ischemic tissue that is likely to infarct, has become one of the most widely used techniques for acute stroke imaging (1-6). Studies have shown that early DWI deficit can be partially salvaged with prompt treatment, consistent with the findings that metabolic disruption within the DWI lesion is heterogeneous (6-11). However, the graded ischemic tissue injury could not be reliably segmented using the percentage reduction of mean diffusivity. There is no well-established imaging method that provides adequate spatiotemporal resolution for the stratification of heterogeneous DWI lesions (12,13). A complementary MRI technique is therefore needed to refine the widely used stroke DWI technique. To this end, diffusion kurtosis, an index that measures non-Gaussian diffusion of water molecules, has been investigated for stroke imaging (14-19). A recent study shows that DWI lesions with no change in mean kurtosis (MK) are likely to respond favorably to early reperfusion while lesions with abnormalities in both mean diffusion (MD) and kurtosis show poor recovery, suggesting that diffusion kurtosis imaging (DKI) is capable of stratifying the heterogeneously injured DWI lesion (20).

As diffusion in cerebral tissue is anisotropic, the standard DKI protocol requires collecting DWI images with multiple b-values along varied diffusion directions, resulting in relatively long acquisition times of 6 minutes or more (15). The scan time has to be substantially shortened before DKI can be used routinely in the acute stroke setting. Hansen et al. recently proposed a fast DKI acquisition and processing approach, and demonstrated its ability to map both mean diffusivity (MD') and apparent mean kurtosis (MK') in fixed brains and control subjects (21). Because it is not practical to obtain and compare different means of DKI in acute stroke patients, our study tested whether the fast DKI approach can characterize heterogeneous ischemic lesions in an animal model of acute stroke prior to clinical translation. We showed that MD' and MK' maps obtained using the fast DKI protocol strongly correlated with MD and MK obtained using conventional approaches, and that the severity and size of diffusion and kurtosis ischemic lesions were in good agreement. Thus, our results demonstrate that the newly proposed fast DKI method is suitable for imaging ischemic stroke in 2 minutes, particularly in the acute stroke setting.

2. METHODS

Animals

Animal experiments were approved by the institutional animal care and use (IACUC, MGH). Adult male Wistar rats (Charles River Laboratory, Wilmington, MA) were anesthetized with 1.5-2.0% isoflurane in air during the experiment. Heart rate and oxygen content of the blood (SpO₂) were monitored (Nonin Pulse Oximeter 8600, Plymouth, MN),

and body temperature was maintained by a circulating warm water jacket positioned around the torso. Ten normal rats and ten stroke rats were imaged, following a standard intraluminal middle cerebral artery occlusion (MCAO) procedure. One stroke rat was excluded from analysis due to failed MCAO preparation with little ischemic lesion.

MRI

MRI scans were performed on a 4.7-Tesla small-bore scanner (Bruker Biospec, Billerica, MA). Multislice MRI (5 slices, slice thickness/gap = 1.8/0.2 mm, field of view = 20x20 mm², acquisition matrix = 48x48) was acquired with single-shot echo-planar imaging (EPI). For the fast DKI protocol, we used 3 b-values: 0, 1000, and 2500 s/mm². One image was obtained for b=0 and three images were obtained for b=1000 s/mm² with the diffusion gradient applied along the directions (1,0,0), (0,1,0) and (0,0,1). In addition, nine images were obtained for b=2500 s/mm² with the diffusion gradient applied along $\mathbf{n}^{(i)}$, $\mathbf{n}^{(i+)}$ and $\mathbf{n}^{(i-)}$, which were defined as $\mathbf{n}^{(1)} = (1,0,0)^T$, $\mathbf{n}^{(1+)} = (0,1,1)$ and $\mathbf{n}^{(1-)} = (0,1,-1)^T$, and similarly for $i=2$ and 3 (gradient pulse duration/diffusion time (δ/Δ) = 6/20 ms, TR/TE = 2500/40.5 ms, number of signal average (NSA) = 4, scan time = 2 min 10 s). Note that superscript i in $\mathbf{n}^{(i)}$ labels the position of the “1” while $\mathbf{n}^{(i+)}$ and $\mathbf{n}^{(i-)}$ it labels the position of the “0” (21).

As we were interested in the mean kurtosis (MK) instead of the full tensor, we extended a conventional diffusion tensor imaging (DTI) protocol for deriving kurtosis (20,22,23). Specifically, we used six b-values: 0, 500, 1000, 1500, 2000, and 2500 s/mm²— in six diffusion gradient directions (scan time = 5 min 10 s). In this study, a conventional mean kurtosis was estimated by averaging the kurtosis from six independent directions, which has been shown in brain to agree fairly well with estimates obtained using higher numbers of directions (22-24). To confirm this, we also obtained DKI using b-values of 0, 1000 and 2500 s/mm² along 15 diffusion directions in four normal rats (scan time = 5 min 10 s) for comparison.

Data Analysis

Images were analyzed in MATLAB (MathWorks, Natick, MA). For the fast DKI acquisition scheme, we calculated MD' using the approach described by Jensen et al. (25). Briefly, we have:

$$MD_{x,y,z} = \frac{(b_1+b_3) D_{x,y,z}^{(12)} - (b_1+b_2) D_{x,y,z}^{(13)}}{b_3 - b_2} \quad (1)$$

where $D_{x,y,z} = \frac{\sum \ln S(b_i)/S(0) - \sum \ln S(b_j)/S(0)}{b_j - b_i}$. We have $MD' = \frac{MD_x + MD_y + MD_z}{3}$, equivalent to the traditional mean diffusivity. MK' was obtained using the method described by Hansen et al. (21)

$$MK' = \frac{\frac{6}{15} \left(\sum_{i=1}^3 \ln \frac{S(b_3, \hat{\mathbf{n}}^{(i)})}{S(0)} + 2 \sum_{i=1}^3 \ln \frac{S(b_3, \hat{\mathbf{n}}^{(i+)})}{S(0)} + 2 \sum_{i=1}^3 \ln \frac{S(b_3, \hat{\mathbf{n}}^{(i-)})}{S(0)} \right) + 6 \cdot b_3 \cdot MD'}{b_3^2 \cdot MD'^2} \quad (2)$$

Note that for the fast DKI approach, MK' was directly calculated (Eq. 2). For processing conventional DKI data, apparent diffusion (D_{app}) and kurtosis coefficients (K_{app}) along each direction were calculated by least-squares fitting DWI signals to

$S(b) = S(0) \cdot e^{-b \cdot D_{app} + \frac{1}{6} b^2 D_{app}^2 K_{app}}$, where $S(b)$ is the DWI signal at a particular b -value and $S(0)$ is the signal without diffusion weighting (22). The mean diffusion coefficient and the kurtosis coefficient were calculated as the average of D_{app} and K_{app} , respectively. For DKI data obtained with fifteen diffusion directions, we used diffusion kurtosis estimator (DKE; <http://academicdepartments.musc.edu/cbi/dki/dke>). To differentiate MD and MK results obtained from these two approaches, we used MD_{mu} and MK_{mu} to denote measurements from six b -values along six directions, and MD_{tf} and MK_{tf} to denote measurements from three b -values along fifteen directions.

3. RESULTS

Fig. 1 shows diffusion and kurtosis maps from the central slice (positioned 2 mm posterior to the bregma) of a representative normal Wistar rat, obtained using the approach of 6 b -values along 6 diffusion directions (Figs. 1 a and b), 3 b -values along 15 directions (Figs. 1 c and d), and the fast acquisition approach (Figs. 1 e and f). Notably, the corpus callosum (CC) and striatum displayed hyperintensity in the MK maps due to their complex/restricted microscopic structure (26). There was significant correlation, per voxel, of the diffusion and kurtosis coefficients measured using six b -values along six directions (MD_{mu} and MK_{mu}) and three b -values along fifteen directions (MD_{tf} and MK_{tf} , squares). Specifically, we have $MD_{tf} = 0.87 \cdot MD_{mu} + 0.08$ ($R^2 = 0.96$, $P < 0.01$, Fig. 1 g) and $MK_{tf} = 0.86 \cdot MK_{mu} + 0.03$ ($R^2 = 0.73$, $P < 0.01$, Fig. 1 h), summarized in Table 1. Analysis of four normal animals with two conventional DKI methods showed that R^2 was 0.96 ± 0.01 for MD_{tf} vs. MD_{mu} , and 0.67 ± 0.09 for MK_{tf} vs. MK_{mu} , respectively, substantially correlated with each other ($P < 0.01$, one sample t -test). In addition, there was significant correlation, per voxel, of the diffusion and kurtosis coefficients measured using six b -values along six directions (MD_{mu} and MK_{mu}) and fast DKI protocols (MD' and MK' , circles). Using linear regression analysis (dashed lines), we found that $MD' = 0.71 \cdot MD + 0.23$ ($R^2_{mu} = 0.79$, $P < 0.01$, Fig. 1 g) and $MK' = 0.74 \cdot MK + 0.15$ ($R^2 = 0.67$, $P < 0.01$, Fig. 1 h). Analysis of all normal animals ($n = 10$) showed that R^2 was 0.76 ± 0.07 for MD' vs. MD_{mu} , and 0.55 ± 0.09 for MK' vs. MK_{mu} respectively, both significantly different from 0 ($P < 0.01$, one sample t -test). The identity lines were plotted in dash dotted lines. In addition, we found kurtosis map SNR in the central slice of normal rats being 6.0 ± 0.4 vs. 6.5 ± 0.7 for the conventional and fast DKI approach, respectively, with their relative difference within 10%. These findings suggest that both diffusion and kurtosis maps can be obtained using the fast DKI acquisition method, in reasonable agreement with the standard approach.

Because the DKI method of multiple b -values along six diffusion directions provides similar DKI measurements as that of three b -values along fifteen directions and has been demonstrated capable of capturing diffusion/kurtosis mismatch, we chose it to test the fast DKI method during acute stroke (20). Fig. 2 compares diffusion and kurtosis maps from the central slice of a representative acute stroke rat obtained using the standard DKI protocol (Figs. 2 a and b) and the fast acquisition approach (Figs. 2 c and d). The right ipsilateral

striatum shows substantial diffusion decrease and kurtosis increase due to ischemic injury. Similar to normal rats, there was significant correlation, per voxel, between diffusion and kurtosis values measured using the standard (MD_{mu} and MK_{mu}) and fast DKI protocols (MD' and MK'). We found that $MD' = 0.90 * MD_{mu} + 0.07$ ($R^2 = 0.82$, $P < 0.01$) and $MK' = 0.88 * MK_{mu} + 0.05$ ($R^2 = 0.80$, $P < 0.01$). The identity lines were included in both figures (dash dotted line). An analysis of all stroke animals ($n=9$) showed that R^2 was 0.80 ± 0.09 and 0.75 ± 0.06 for MD' vs. MD_{mu} and MK' vs. MK_{mu} , respectively, significantly different from zero ($P < 0.01$, one sample t-test).

Fig. 3 shows multi-slice diffusion and kurtosis maps from a representative acute stroke rat. Diffusion and kurtosis lesions in the ipsilateral ischemic brain were determined if their values were two standard deviations beyond their means. Diffusion and kurtosis images and outlined lesions were shown for the conventional method (Figs. 3a and 3b) and fast DKI approach (Figs. 3c and 3d), demonstrating that the threshold-based tissue segmentation algorithm can provide reasonable delineation of heterogeneous ischemic tissue.

We compared diffusion and kurtosis lesion size determined using the fast DKI method and the conventional DKI protocol (Fig. 4). Diffusion and kurtosis lesion volumes were $130 \pm 85 \text{ mm}^3$ and $91 \pm 55 \text{ mm}^3$, respectively, from the conventional method while they were $140 \pm 102 \text{ mm}^3$ and $106 \pm 76 \text{ mm}^3$ from the fast DKI method. Regression analysis shows MD' lesion = $1.18 * MD_{mu}$ lesion - 13.74 mm^3 ($R^2 = 0.98$, $P < 0.01$, Pearson Correlation), and MK' lesion = $1.38 * MK_{mu}$ lesion - 19.32 mm^3 ($R^2 = 0.98$, $P < 0.01$, Pearson Correlation). Paired t-test showed no significant difference in diffusion lesion size ($P > 0.19$) and kurtosis lesion size ($P > 0.08$). Importantly, there was no significant difference in kurtosis/diffusion lesion mismatch obtained from these two methods ($26 \pm 13\%$ vs. $23 \pm 8\%$, $P > 0.08$). In addition, regression analysis showed significant correlation in their kurtosis/diffusion lesion mismatch ($R^2 = 0.57$, $P < 0.02$). Consequently, our data confirmed that the fast DKI protocol provided good measurement of diffusion and kurtosis during acute stroke, in good agreement with the conventional DKI protocol.

We further compared MD' and MK' values in contralateral normal region, diffusion and kurtosis lesions (Fig. 5). One-way analysis of variance (ANOVA) with Bonferroni correction was performed to compare diffusion and kurtosis values in contralateral normal area, ipsilateral ischemic diffusion and kurtosis lesions. The contralateral normal MD' and MK' were determined to be $0.87 \pm 0.02 \text{ } \mu\text{m}^2/\text{ms}$ and 0.64 ± 0.03 , respectively. For MD' lesion, we found MD' and MK' being $0.67 \pm 0.07 \text{ } \mu\text{m}^2/\text{ms}$ and 0.89 ± 0.05 , respectively, significantly different from those of the contralateral normal region ($P < 0.01$). For MK' lesion, we found MD' and MK' being $0.69 \pm 0.07 \text{ } \mu\text{m}^2/\text{ms}$, and 0.97 ± 0.08 , respectively, significantly different from those of the contralateral normal region ($P < 0.01$). Notably, MD' was not statistically different between MD' and MK' lesions while their MK' was significantly different ($P = 0.02$), consistent with the notion that the severity of mean diffusivity decrease could not reliably stratify the heterogeneous DWI lesion (12).

4. DISCUSSION

It has been shown that DKI is able to stratify heterogeneously injured DWI lesions, thus enabling improved definition of ischemic penumbra (20). However, the relatively long acquisition time of the technique limits its use in the acute stroke setting (15,19). Hansen et al. demonstrated that fast DKI approach strongly correlates with an approach of multiple b-values along fully sampled diffusion directions in normal subjects. Specifically, the fast DKI protocol used in our study took about 2 min, substantially shorter than the conventional DKI protocols of 5 min. Before we can apply it to study patients in the acute stroke setting, it is necessary to compare it with conventional DKI methods and validate that diffusion and kurtosis lesions can be reliably measured at reduced scan time. It is important to note that MD and MD' correspond to the same physical quantities, albeit estimated in different ways. In contrast, MK and MK' are physically distinct, but are nonetheless highly correlated. Specifically, MK presents the directional average of the kurtosis and MK' represents the average of the kurtosis tensor (21). Indeed, we showed that mean diffusion and kurtosis coefficients obtained using the fast DKI scheme substantially correlated with those from conventional DKI protocols (Figs. 1 and 2). In addition, the fast DKI method was in excellent agreement with the standard methods in defining mean diffusion and kurtosis lesions (Fig. 4). More importantly, the kurtosis/diffusion lesion mismatch during acute ischemic stroke can be captured using the fast DKI method (21).

As the MK measurement was the major focus in our study instead of the full kurtosis tensor, we chose the approach of multiple b-values along six undersampled diffusion directions in order to reduce its scan time for acute stroke imaging. We derived kurtosis using goodness-of-fit, a model which has also been used by Lätt et al. and Jensen et al (22,23,25). The small number of diffusion directions used for conventional DKI is a limitation of the study. In particular, the MK measurements determined from 6 directions are probably more variable and less accurate than would be the case for a 30 direction protocol (21). Recently, Fukunaga et al. demonstrated similar MK measurements using 6 and 15 directions (24). Our results also confirmed significant correlation between measurements obtained with six b-values along six directions, three b-values along fifteen directions and the fast DKI method proposed by Hansen et al (21). Both diffusion and kurtosis determined from the fast method were slightly underestimated with respect to the approach of multiple b-values. The reasons for this could be complex because in vivo diffusion measurements depend on a number of parameters, including the diffusion direction, number and range of b-values as well as diffusion time. In addition, the fast approach solves for the diffusion and kurtosis by assuming negligible high order diffusion (e.g., $O(b^3)$) and Rician noise terms, while such terms could be treated as the residual fitting error in the multiple-b DKI approach. Importantly, the correlation between these two protocols was highly significant. It is worth noting that the fast DKI approach only provides measurements of mean diffusion and kurtosis, which may hinder the adoption of fast DKI protocol in the situation where a complete set of diffusion tensor metrics beyond mean diffusion and kurtosis are required (19,26-33). Because studies have demonstrated that diffusion anisotropic matrixes such as FA do not consistently show changes in the first six hours of ischemic stroke, the fast DKI approach, despite the loss of its ability to resolve diffusion and kurtosis tensors, should be

acceptable for the acute stroke imaging application where imaging time has to be minimized (35,36).

The establishment of fast DKI protocol should enable future studies to investigate early ischemic tissue injury in the acute stroke setting, verify whether kurtosis MRI augments standard stroke MRI, and ultimately provides a guidance for more effective stroke treatment. Our study used an intraluminal stroke model, which provides relatively reproducible ischemic insult, to validate the fast DKI MRI method in acute stroke. However, the intraluminal MCAO induces severe hypoperfusion and aggravates ischemic injury, which could shorten the therapeutic window. The biological significance of heterogeneous kurtosis/diffusion mismatch should be elucidated using thromboembolic animal stroke models, which better mimic human ischemic stroke than intraluminal stroke models. In addition, it is necessary to develop more advanced tissue classification algorithms – beyond the threshold-based analysis – to quickly and accurately segment ischemic tissue in guiding stroke treatment (34-36).

5. CONCLUSION

Our study evaluated a fast DKI acquisition method for acute stroke imaging and showed that the size and severity of diffusion and kurtosis lesions obtained using the fast method substantially correlated with those obtained using a conventional DKI protocol. Therefore, the fast stroke DKI approach holds great promise for investigation of the evolution and therapeutic relevance of diffusion and kurtosis lesions, and ultimately for facilitating translational kurtosis imaging in the acute stroke setting.

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REFERENCES

1. Moseley M, Kucharczyk J, Mintorovitch J, Cohen Y, Kurhanewicz J, Derugin N, Asgari H, Norman D. Diffusion-weighted MR imaging of acute stroke: correlation with T2-weighted and magnetic susceptibility-enhanced MR imaging in cats. *Am J Neuroradiol.* 1990; 11(3):423–429. [PubMed: 2161612]
2. Chien D, Kwong KK, Gress DR, Buonanno FS, Buxton RB, Rosen BR. MR diffusion imaging of cerebral infarction in humans. *AJNR Am J Neuroradiol.* 1992; 13(4):1097–1102. discussion 1103-1095. [PubMed: 1636519]
3. Warach S, Chien D, Li W, Ronthal M, Edelman R. Fast magnetic resonance diffusion-weighted imaging of acute human stroke. *Neurology.* 1992; 42(9):1717–1723. [PubMed: 1513459]
4. Neumann-Haefelin T, Wittsack HJ, Wenserski F, Siebler M, Seitz RJ, Modder U, Freund HJ. Diffusion- and perfusion-weighted MRI. The DWI/PWI mismatch region in acute stroke. *Stroke.* 1999; 30(8):1591–1597. [PubMed: 10436106]
5. Parsons MW, Barber PA, Chalk J, Darby DG, Rose S, Desmond PM, Gerraty RP, Tress BM, Wright PM, Donnan GA, Davis SM. Diffusion- and perfusion-weighted MRI response to thrombolysis in stroke. *Ann Neurol.* 2002; 51(1):28–37. [PubMed: 11782981]
6. Kidwell CS, Alger JR, Saver JL. Beyond mismatch: evolving paradigms in imaging the ischemic penumbra with multimodal magnetic resonance imaging. *Stroke.* 2003; 34(11):2729–2735. [PubMed: 14576370]

7. Nicoli F, Lefur Y, Denis B, Ranjeva JP, Confort-Gouny S, Cozzzone PJ. Metabolic counterpart of decreased apparent diffusion coefficient during hyperacute ischemic stroke: a brain proton magnetic resonance spectroscopic imaging study. *Stroke*. 2003; 34(7):e82–87. [PubMed: 12817104]
8. Sun PZ, Wang EF, Cheung JS. Imaging acute ischemic tissue acidosis with pH-sensitive endogenous amide proton transfer (APT) MRI – Correction of tissue relaxation and concomitant RF irradiation effects toward mapping quantitative cerebral tissue pH. *Neuroimage*. 2012; 60(1):1–6. [PubMed: 22178815]
9. Sun PZ, Cheung JS, Wang EF, Lo EH. Association between pH-weighted endogenous amide proton chemical exchange saturation transfer MRI and tissue lactic acidosis during acute ischemic stroke. *J Cereb Blood Flow Metab*. 2011; 31(8):1743–1750. [PubMed: 21386856]
10. Guadagno JV, Warburton EA, Jones PS, Day DJ, Aigbirhio FI, Fryer TD, Harding S, Price CJ, Green HA, Barret O, Gillard JH, Baron JC. How affected is oxygen metabolism in DWI lesions?: A combined acute stroke PET-MR study. *Neurology*. 2006; 67(5):824–829. [PubMed: 16966545]
11. Sun PZ, Zhou J, Sun W, Huang J, van Zijl PC. Detection of the ischemic penumbra using pH-weighted MRI. *J Cereb Blood Flow Metab*. 2007; 27(6):1129–1136. [PubMed: 17133226]
12. Fiehler J, Foth M, Kucinski T, Knab R, von Bezold M, Weiller C, Zeumer H, Rother J. Severe ADC decreases do not predict irreversible tissue damage in humans. *Stroke*. 2002; 33(1):79–86. [PubMed: 11779893]
13. Ringer TM, Neumann-Haefelin T, Sobel RA, Moseley ME, Yenari MA. Reversal of early diffusion-weighted magnetic resonance imaging abnormalities does not necessarily reflect tissue salvage in experimental cerebral ischemia. *Stroke*. 2001; 32(10):2362–2369. [PubMed: 11588327]
14. Cheung MM, Hui ES, Chan KC, Helpen JA, Qi L, Wu EX. Does diffusion kurtosis imaging lead to better neural tissue characterization? A rodent brain maturation study. *Neuroimage*. 2009; 45(2):386–392. [PubMed: 19150655]
15. Jensen JH, Falangola MF, Hu C, Tabesh A, Rapalino O, Lo C, Helpen JA. Preliminary observations of increased diffusional kurtosis in human brain following recent cerebral infarction. *NMR Biomed*. 2011; 24(5):452–457. [PubMed: 20960579]
16. Grinberg F, Ciobanu L, Farrher E, Shah NJ. Diffusion kurtosis imaging and log-normal distribution function imaging enhance the visualisation of lesions in animal stroke models. *NMR in Biomedicine*. 2012; 25(11):1295–1304. [PubMed: 22461260]
17. Hui ES, Du F, Huang S, Shen Q, Duong TQ. Spatiotemporal dynamics of diffusional kurtosis, mean diffusivity and perfusion changes in experimental stroke. *Brain Research*. 2012; 1451(0):100–109. [PubMed: 22444274]
18. Song Y, Cho H, Hopper T, Pomerantz A, Sun PZ. Magnetic resonance in porous media: recent progress. *J Chem Phys*. 2008; 128(5):052212. [PubMed: 18266417]
19. Hui ES, Fieremans E, Jensen JH, Tabesh A, Feng W, Bonilha L, Spampinato MV, Adams R, Helpen JA. Stroke Assessment With Diffusional Kurtosis Imaging. *Stroke*. 2012; 43(11):2968–2973. [PubMed: 22933581]
20. Cheung JS, Wang E, Lo EH, Sun PZ. Stratification of heterogeneous diffusion MRI ischemic lesion with kurtosis imaging – Evaluation of mean diffusion and kurtosis MRI mismatch in an animal model of transient focal ischemia. *Stroke*. 2012; 43(8):2252–2254. [PubMed: 22773558]
21. Hansen B, Lund TE, Sangill R, Jespersen SN. Experimentally and computationally fast method for estimation of a mean kurtosis. *Magn Reson Med*. 2013; 69(6):1754–1760. [PubMed: 23589312]
22. Jensen JH, Helpen JA, Ramani A, Lu H, Kaczynski K. Diffusional kurtosis imaging: The quantification of non-gaussian water diffusion by means of magnetic resonance imaging. *Magn Reson Med*. 2005; 53(6):1432–1440. [PubMed: 15906300]
23. Lätt J, Nilsson M, Wirestam R, Johansson E, Larsson E-M, Stahlberg F, Brockstedt S. In vivo visualization of displacement-distribution-derived parameters in q-space imaging. *Magn Reson Imaging*. 2008; 26(1):77–87. [PubMed: 17582719]
24. Fukunaga I, Hori M, Masutani Y, Hamasaki N, Sato S, Suzuki Y, Kumagai F, Kosuge M, Hoshito H, Kamagata K, Shimoji K, Nakanishi A, Aoki S, Senoo A. Effects of diffusional kurtosis imaging parameters on diffusion quantification. *Radiol Phys Technol*. 2013; 6(2):343–348. [PubMed: 23536232]

25. Jensen JH, Helpern JA. MRI quantification of non-Gaussian water diffusion by kurtosis analysis. *NMR Biomed.* 2010; 23(7):698–710. [PubMed: 20632416]
26. Hui ES, Cheung MM, Qi L, Wu EX. Towards better MR characterization of neural tissues using directional diffusion kurtosis analysis. *Neuroimage.* 2008; 42(1):122–134. [PubMed: 18524628]
27. Raab P, Hattingen E, Franz K, Zanella FE, Lanfermann H. Cerebral gliomas: diffusional kurtosis imaging analysis of microstructural differences. *Radiology.* 2010; 254(3):876–881. [PubMed: 20089718]
28. Wang JJ, Lin WY, Lu CS, Weng YH, Ng SH, Wang CH, Liu HL, Hsieh RH, Wan YL, Wai YY. Parkinson Disease: Diagnostic Utility of Diffusion Kurtosis Imaging. *Radiology.* 2011; 261(1): 210–217. [PubMed: 21771952]
29. Grossman EJ, Ge Y, Jensen JH, Babb JS, Miles L, Reaume J, Silver JM, Grossman RI, Inglese M. Thalamus and Cognitive Impairment in Mild Traumatic Brain Injury: A Diffusional Kurtosis Imaging Study. *J Neurotrauma.* 2011; 29(13):2318–2327. [PubMed: 21639753]
30. Grinberg F, Farrher E, Kaffanke J, Oros-Peusquens A-M, Shah NJ. Non-Gaussian diffusion in human brain tissue at high b-factors as examined by a combined diffusion kurtosis and biexponential diffusion tensor analysis. *NeuroImage.* 2011; 57(3):1087–1102. [PubMed: 21596141]
31. Van Cauter S, Veraart J, Sijbers J, Peeters RR, Himmelreich U, De Keyser F, Van Gool SW, Van Calenbergh F, De Vleeschouwer S, Van Hecke W, Sunaert S. Gliomas: Diffusion Kurtosis MR Imaging in Grading. *Radiology.* 2012; 263(2):492–501. [PubMed: 22403168]
32. Rosenkrantz AB, Sigmund EE, Winnick A, Niver BE, Spieler B, Morgan GR, Hajdu CH. Assessment of hepatocellular carcinoma using apparent diffusion coefficient and diffusion kurtosis indices: preliminary experience in fresh liver explants. *Magn Reson Imaging.* 2012; 30(10):1534–1540. [PubMed: 22819175]
33. Fieremans E, Jensen JH, Helpern JA. White matter characterization with diffusional kurtosis imaging. *NeuroImage.* 2011; 58(1):177–188. [PubMed: 21699989]
34. Jacobs MA, Knight RA, Soltanian-Zadeh H, Zheng ZG, Goussev AV, Peck DJ, Windham JP, Chopp M. Unsupervised segmentation of multiparameter MRI in experimental cerebral ischemia with comparison to T2, diffusion, and ADC MRI parameters and histopathological validation. *J Magn Reson Imaging.* 2000; 11(4):425–437. [PubMed: 10767072]
35. Shen Q, Ren H, Fisher M, Duong TQ. Statistical prediction of tissue fate in acute ischemic brain injury. *J Cereb Blood Flow Metab.* 2005; 25(10):1336–1345. [PubMed: 15829912]
36. Wu O, Sumii T, Asahi M, Sasamata M, Ostergaard L, Rosen BR, Lo EH, Dijkhuizen RM. Infarct prediction and treatment assessment with MRI-based algorithms in experimental stroke models. *J Cereb Blood Flow Metab.* 2007; 27(1):196–204. [PubMed: 16685257]

Fig. 1.

Comparison of diffusion kurtosis maps obtained using different DKI protocols from a normal Wistar rat. MD_{mu} map (a) and MK_{mu} map (b) from the approach of multiple b-values along undersampled diffusion direction. MD_{tf} map (c) and MK_{tf} map (d) from the approach of three b-values along 15 diffusion direction. e) MD' map from the fast DKI method. f) MK' map from the fast DKI method. g) Voxel-wise correlation between mean diffusivity, MD_{mu} vs. MD_{tf} (gray squares and dashed line) and MD_{mu} vs. MD' (black circles and dashed line). The identity line is shown in black dash-dotted line. h) Voxel-wise correlation test between mean kurtosis, MK_{mu} vs. MK_{tf} (gray squares and dashed line) and MK_{mu} vs. MK' (black circles and dashed line).

Fig. 2.

Comparison of mean diffusion and mean kurtosis maps in an animal model of acute ischemic stroke. a) MD_{mu} map. b) MK_{mu} map. c) MD' map. d) MK' map. e) Voxel-wise correlation between MD_{mu} and MD' (circles and dashed line), and the identity line is shown in black dash-dotted line. f) Voxel-wise correlation between MK_{mu} and MK' (circles and dashed line), and the identity line is shown in black dash-dotted line.

Fig. 3. MD_{mu} (a) and MK_{mu} (b) images obtained from a conventional DKI method from a representative acute stroke rat. MD' (c) and MK' (d) images obtained from the fast DKI method. Lesions were outlined using a threshold-based tissue segmentation algorithm.

Fig. 4.

Comparison of lesion size from mean diffusivity and mean kurtosis images determined from the approach of multiple b-values along undersampled diffusion directions and the fast DKI approach. a) MD_{mu} vs. MD' lesion size, with the linear regression shown in dotted line, and the identity line is shown in black dash-dotted line. b) MK_{mu} vs. MK' lesion size, with the linear regression shown in dotted line, and the identity line is shown in black dash-dotted line.

Fig. 5.

Comparison of diffusion values (a) and kurtosis values (b) in contralateral normal area, ipsilateral ischemic diffusion and kurtosis lesions. Significant MD' decrease was found in MD' and MK' lesions from the contralateral normal area, without significant change between MD' and MK' lesions. In comparison, there is significant MK' increase from the normal areas, with significant MK' difference between MD' and MK' lesions.

Table 1

Summary of linear regression between diffusion and kurtosis measured using the approach of 3 b-values along 15 directions (MD_{tf} and MK_{tf}), fast DKI approach (MD' and MK') and 6 b-values along 6 diffusion directions (MD_{mu} and MK_{mu}).

	Diffusion ($\mu m^2/ms$)	Kurtosis
DKI (3 b-values, 15-directions) (MD_{tf} and MK_{tf})	$MD_{tf}=0.87*MD_{mu}+0.08$ ($R^2=0.96$, $P<0.01$)	$MK_{tf}=0.86*MK_{mu}+0.03$ ($R^2=0.73$, $P<0.01$)
Fast DKI (MD' and MK')	$MD'=-0.71*MD_{mu}+0.23$ ($R^2=0.79$, $P<0.01$)	$MK'=-0.74*MK_{mu}+0.15$ ($R^2=0.67$, $P<0.01$)