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Manifestation and Post-hoc Correction of Gradient Cross-term Artifacts in DTI

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Abstract

Cross-terms between imaging and diffusion gradients, unaccounted for during tensor calculations, can lead to erroneous estimation of diffusivity and fractional anisotropy (FA) in regions of isotropic and anisotropic diffusion. Cross-term of magnitude 136.8 ± 1.6 s/mm², artificially introduced in the slice-encode direction caused an increase in fractional anisotropy (FA) in isotropic phantom from 0.0546 ± 0.0001 to 0.0996 ± 0.0001 , while the change in chimpanzee brain depended on the orientation of the white matter (WM). Mean diffusivity (MD), remained unchanged in isotropic phantom, but increased by ~20% in the WM due to cross-terms. A bias was observed in the principal eigenvectors in both phantom and chimpanzee brain, resulting in significant increase in midline crossing fibers along the bias than perpendicular to it in tractography in chimpanzee brain. Post-hoc correction of these artifacts was achieved by estimating the cross-term factors using calibration scans on an isotropic phantom and modifying the b-matrix before tensor calculation. Upon correction, the FA and MD values closely resembled the values obtained from sequence without cross-terms, and the bias in principal eigenvectors was eliminated. Customized sequences involving large b-values, high-resolution imaging, or long diffusion or echo times should therefore be evaluated and any residual cross-terms corrected before implementation.

Keywords

Diffusion tensor imaging; Artifacts in MRI; Gradient cross-terms; Post-processing correction

Introduction

Signal attenuation due to diffusion in diffusion-weighted images (DWI) depends not only on the diffusion gradients, but also on imaging gradients and interactions between them (gradient cross-terms). While signal attenuation due to imaging gradients exist in diffusion weighted images (DWIs) as well as reference image (B0), signal attenuation due to diffusion gradients and cross-terms are present only in DWIs. Moreover, unlike signal attenuation due to diffusion gradients, those due to cross-terms depend on the angle between the diffusion and imaging gradient directions in isotropic samples. Therefore, gradient cross-term not

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accounted for during tensor calculations can cause an artificial increase in fractional anisotropy (FA) in isotropic samples and a bias in anisotropic samples. Other tensor parameters such as MD and eigenvectors are also affected by cross-terms (1,2).

The degree of signal attenuation in DWI depends on the b-factor, which can be estimated mathematically by knowing the strength and timing of gradients used to realize the protocol parameters in the pulse sequence. The b-factor in diffusion tensor imaging (DTI) is expressed as a 3×3 matrix (b-matrix) (3), with diagonal elements representing the b-factor from all gradient effects in each of the read-, phase-, and slice-encoding directions. Off-diagonal terms of the b-matrix represent attenuation factor arising from gradients applied along one axis with each of the gradients applied along the other axes. These off-diagonal terms of the b-matrix can be ignored for the calculation of diffusion parameters in a purely isotropic media, but not for anisotropic sample such as the brain (3–5). Furthermore, the gradient cross-terms effects each term in the b-matrix, thereby affecting calculations in both the isotropic and anisotropic samples (6–9).

The b-matrix for each DWI is often calculated within the pulse sequence and stored in image header files for later use in tensor reconstruction. However, some customized sequences may not have the correct b-matrix in the header that can be used for image format conversion and rely on the b-value and b-vectors derived from the diffusion gradient table for tensor calculations. Furthermore, tensor reconstruction software such as FSL (FMRIB, UK) or DTIstudio (F. M. Kirby Research Center for Functional Brain Imaging, Baltimore, MD) does not require the b-matrix for each DWI, but derive it from the gradient-table based b-value and b-vector files output from the image conversion algorithms. While this would be a sufficient approximation of the actual b-matrix in routine applications, specialized sequences like q-ball (which use large b-values), high spatial resolution DTI (which use relatively large imaging gradients), and long diffusion time sequences (which have higher gradient interactions due to longer time interval between gradients) can be adversely affected by the greater interaction between imaging and diffusion gradients. Therefore the b-matrix of such sequences should account for additional gradient cross-terms factors in the tensor reconstruction.

In this study, we demonstrate the importance of evaluating customized pulse sequences for errors in FA and MD introduced by uncompensated gradient cross-terms, and also provided a means of correcting these errors post-acquisition using a calibration scan on isotropic phantom. First, an echo-planar DTI sequence was modified (Fig 1a) to introduce non-negligible gradient cross-terms and their effects on DWIs and reconstructed tensors were evaluated. A calibration scan was performed with this modified sequence on an isotropic phantom with identical imaging protocols but with diffusion gradients applied only along the positive and negative directions in each of the read-, phase-, and slice-encoding directions to calculate the cross-term factors. Finally, the b-matrix was modified with the calculated cross-term factors and the new diffusion tensors reconstructed in Matlab (Mathworks incorporated, Natick, MA). The tensors reconstructed from an isotropic phantom and a chimpanzee brain, before and after cross-term corrections were compared to that of a sequence with cross-terms properly accounted for. Such calibration scans can be useful in studies using specialized and/or custom DTI sequences to determine the presence of, and correct for gradient cross-term errors in their DTI sequences. Determining and correcting for these errors may be especially critical in studies of brain lateralization.

Theory

The signal attenuation in DWI is given by $S = S_0 e^{-\left(\sum_{i=1}^3 \sum_{j=1}^3 b_{ij} D_{ij}\right)}$ where S_0 is the reference signal intensity (acquired without diffusion gradients), b_{ij} is the b-matrix, and D_{ij} is the anisotropic diffusivity of the medium. Each element of the b-matrix can be split into its contributions from diffusion gradients, imaging gradients and cross-terms between the two as $a_1 * G_d^2 + a_2 * G_d * G_i + a_3 * G_i^2$, where G_d and G_i are diffusion and imaging gradients and a_1 , a_2 , and a_3 are constants depending on gradient timing and gyromagnetic ratio (6,10). The signal attenuation due to imaging gradients can be ignored if the reference images are acquired with the same imaging parameters, as is usually the case.

The gradient cross-terms affecting each of the read-, phase-, and slice-encoding directions can be obtained from two DWIs acquired with exactly the same imaging protocols and diffusion gradients pointing in the positive and negative encode directions in an isotropic medium (7,10)

$$[a_2 G_d G_i]_{1,2,3} = \frac{\ln \left(\left[\frac{S_{b+}}{S_{b-}} \right]_{1,2,3} \right)}{2D} \quad [1]$$

where 1, 2, and 3 are the read-, phase-, and slice-encoding directions and D is the known diffusivity of the isotropic sample.

The b-matrix should ideally be calculated as an integral of the contribution of each gradient in the pulse sequence for every diffusion direction. In the absence of information for calculating the b-matrix exactly, contributions from diffusion and cross-terms can be calculated from the b-value and diffusion gradient table used for imaging, as well as the calibration scan. Contribution of the diffusion gradients towards b-value in a double spin echo sequence can be calculated by (11)

$$b = \gamma^2 G^2 \left(\delta^2 \left(\Delta - \frac{\delta}{3} \right) - 2d\delta\delta_2 + d \left(\delta_2^2 + \delta_2'^2 \right) \right) \quad [2]$$

where γ is the gyromagnetic ratio, G is the diffusion gradient strength, Δ the interpulse duration between the first and third gradient pulses in Fig. 1a, δ the total duration of the first and second diffusion gradient pulses, d the duration from end of first pulse to start of second pulse, and δ_2 and δ_2' the durations of the second and fourth pulses, respectively. The b-matrix for diffusion gradients is given simply as (after rearranging terms)

$$\bar{b}_{d,ii} = b \begin{bmatrix} g_{1,ii}^2 & g_{2,ii}^2 & g_{3,ii}^2 & 2g_{1,ii}g_{2,ii} & 2g_{1,ii}g_{3,ii} & 2g_{2,ii}g_{3,ii} \end{bmatrix}^T \quad [3]$$

where $b_{d,ii}$ is the contribution to diffusion matrix from diffusion gradients corresponding to the ii^{th} diffusion direction, $g_{j,ii}$ is the b-vector along the j^{th} encoding direction corresponding to the ii^{th} diffusion direction. Similarly, the contribution of gradient cross-terms towards b-matrix (9) is given by

$$\bar{b}_{c,ii} = [[a_2 G_d G_i]_1 g_{1,ii} [a_2 G_d G_i]_2 g_{2,ii} [a_2 G_d G_i]_3 g_{3,ii} \\ 2([a_2 G_d G_i]_1 g_{1,ii} + [a_2 G_d G_i]_2 g_{2,ii}) 2([a_2 G_d G_i]_1 g_{1,ii} + [a_2 G_d G_i]_3 g_{3,ii}) 2([a_2 G_d G_i]_2 g_{2,ii} + [a_2 G_d G_i]_3 g_{3,ii})]^T \quad [4]$$

Total b-matrix is simply

$$\bar{b}_{ii} = \bar{b}_{d,ii} + \bar{b}_{e,ii}. \quad [5]$$

The diffusivity diffusion tensor matrix D were, can then be determined by the best fit solution (12,13) given by

$$D = (\bar{b}^T \bar{b})^{-1} \bar{b}^T S \quad [6]$$

where S is the signal vector given by $S_{ii} = -\ln\left(\frac{S_{DWI,ii}}{S_{0,ii}}\right)$, calculated on a pixel-by-pixel basis. The fractional anisotropy (FA), and mean diffusivity (MD) were calculated from the eigenvalues of the D -matrix. White matter fiber tractography was performed using FSL, with the b -values and b -vectors for FSL derived from the b -matrix using

$$b\text{-value}_{ii} = \text{norm}(b\text{-matrix}_{ii}) \text{ and } b\text{-vector}_{ii} = \text{resultant}(b\text{-matrix}_{ii}) \quad [7]$$

Materials and Method

Animal preparation

MRI was performed on one adult chimpanzee (*Pan troglodytes*, age 18 years, weight 90 kgs) in accordance with guidelines approved by the Institutional Animal Care and Use Committee of Emory University. The chimpanzee was anesthetized with an injection of ketamine/xylazine (4 mg/kg, i.m.) during preparation, and maintained under propofol anesthesia (10 mg/kg/hr, i.v.) during imaging, under the veterinary supervision. The chimpanzee was intubated and physiology (respiratory rate and depth, EtCO₂, and heart rate) monitored throughout the experiment.

MR imaging

Images were acquired on a Siemens 3T Trio scanner (Siemens Medical System, Malvern, PA), with a standard birdcage coil. A product DTI sequence based on double-spin echo EPI sequence (*no_XT*) was modified to introduce gradient cross-term along the slice-encode direction by moving the rephase lobe of the slice-select gradient (*XT*, Fig. 1A). Images were acquired from an isotropic phantom (1 M mannitol + 0.1 M creatine dissolved in distilled water) and an *in-vivo* adult chimpanzee brain using both the *no_XT* and *XT* sequences, with exactly the same imaging parameters without changing any of the other gradients. However, the scans on the chimpanzee with *no_XT* and *XT* sequences were performed during separate imaging sessions, as part of a larger investigation into cortico-spinal asymmetry and handedness (14). The imaging parameters were TR = 5740 ms, TE = 91 ms, slice thickness = 1.8 mm, FOV = 230×230 mm², imaging matrix = 128×128, in-plane resolution = 1.8×1.8 mm², receiver bandwidth = 1954 Hz/Px, and number of averages = 1. Reference image (B_0) was acquired with diffusion gradients switched off, and DWIs were acquired with $b = 1000$ s/mm² and diffusion gradients rotated in 60 directions to uniformly cover a unit hemisphere. In addition, a calibration scan was performed on the isotropic phantom with the same imaging protocol parameters and $b = 1000$ s/mm² but with diffusion gradients along only in 6 directions, namely, positive and negative direction in each of the read-, phase-, and slice-encoding axes.

Cross-term correction and DTI reconstruction

Background extraction (using BET function in FSL) and eddy-current and movement correction using affine registration were performed on all images before analysis. The effect

of gradient cross-terms was first evaluated by plotting the signal variation as well as ADC from the isotropic phantom as the diffusion gradients were rotated. DTI parameters were reconstructed from images obtained with both *no_XT* and *XT* sequences using FDT toolbox in FSL (DTIFIT). Reconstructed FA and MD were visualized in FSLVIEW. Direction of principal eigenvector was visualized in FSLVIEW in color, modulated with FA signal intensity, and overlaid with line representation of its direction.

Gradient cross-terms along the three encoding axes were calculated from the calibration scan on the isotropic phantom using equation [1], and the cross-term factors obtained were used to perform cross-term correction. A new b-matrix was created in Matlab using diffusion gradient strength and timing information as well as cross-term factors according to equations [2] through [5], and diffusivity matrix reconstructed with equation [6], and DTI parameters were reconstructed from the diffusivity matrix in Matlab as described (*XT_corr1*). The reconstructed DTI maps were visualized as described for the *no_XT* and *XT* sequences. Next, b-values and b-vectors were derived using equation [7] for input into FSL scripts (*XT_corr2*).

ROI comparison

An ROI covering all 41 slices was drawn within the isotropic phantom, and average FAs and MDs from *no_XT*, *XT*, and *XT_corr1* were compared. Furthermore, histogram of FA values within the ROI was plotted and compared.

The FA and MD images obtained from chimpanzee using *no_XT*, *XT*, *XT_corr1*, and *XT_corr2* were coregistered in FSL, and white matter (WM) skeletons were generated at a threshold of 0.2. A WM ROI was created at the intersection of the WM skeleton (SKELETONIZE function in FSL) run on FA images and a hand drawn mask on the internal capsule (IC). Average FA and MD from all four reconstructions were compared. Finally, two seed-masks were drawn each on the left- and right-cerebral peduncle (CP) in the chimpanzee FA, and tractography was performed from each mask in FSL with parameters of 5000 samples, 0.2 curvature threshold, 2000 steps with length of 0.5 mm (BEDPOSTX and then single mask option in PROBTRACKX). The number of pseudo-tracks (as counted by the FSL software) crossing from the left to right (seed mask of left CP) and from right to left (seed mask of right CP) through the corpus callosum at a single midline section was determined as a percentage of the waytotal (total number of fibers generated) from *no_XT*, *XT* and *XT_corr2*. Tensors derived from *XT_corr1* were not evaluated in this way as algorithms for BEDPOSTX and tractography were not implemented in Matlab.

Results

Phantom scans

A double spin-echo echo-planar DTI sequence was implemented with misplaced slice-select rephase gradient pulse (Fig. 1a). The signal to noise ratio in B0 images obtained from the isotropic DTI phantom was marginally reduced, from 46.5 ± 0.6 in the *no_XT* to 44.3 ± 0.4 in the *XT* sequence ($p=0.003$, $n=41$ slices). As the diffusion gradient direction was changed, the signal intensity of the diffusion weighted images varied between 20.16% to 20.84% of B0 signal intensity ($20.51 \pm 0.02\%$) in the *no_XT* sequence, and 17.82% to 23.88% in the *XT* sequence ($20.52 \pm 0.021\%$, Fig. 1b). While the percent signal intensity changes were not statistically significant ($p=0.95$, $n=60$ directions, paired t-test) from each other, there was considerably more variation in the *XT* sequence.

DTI maps of the isotropic phantom (Fig. 2a and 2b) were reconstructed from DWI acquired from the *no_XT* and *XT* sequences using the FDT toolbox in FSL as well as Matlab scripts written in-house. The FA was low and principal eigenvectors were randomly oriented in

DTI reconstructed from the *no_XT sequence* as expected. However, color map of the principal eigenvector, modulated by the magnitude of FA, showed a purple tinge in the DTI reconstructed from the *XT sequence*, with the principal eigenvector pointing diagonally across in sagittal images and vertically in the axial images.

Cross-terms derived from the calibration scans showed significant uncompensated effects in the slice direction amounting to a b-value of $136.8 \pm 1.6 \text{ s/mm}^2$. The cross-terms in other directions were much lower, at $9 \pm 5.8 \text{ s/mm}^2$ and $2.3 \pm 9 \text{ s/mm}^2$ for read- and phase-encoding directions, respectively. The b-value contributions from the cross-terms were applied to calculate the b-matrix for *XT_corr1* as well as the b-values and b-vectors for *XT_corr2*. The new average b-value thus calculated was slightly higher than 1000 s/mm^2 at $1042.8 \pm 10 \text{ s/mm}^2$, and varied between 868 s/mm^2 and 1231 s/mm^2 as a function of diffusion direction. The minimum b-value was obtained when the diffusion gradients were applied in the directions that were 151 and 171 degrees away from the positive slice encode axis, respectively and the maximum b-value was seen when the diffusion gradients were applied in directions 14 and 26 degrees from the positive slice encode axis. Upon correction, the primary eigenvectors were once again randomly oriented (Fig. 2a and 2b).

ADC was calculated from DWI acquired with each diffusion gradient direction. Large variations were observed in the ADCs calculated from DWIs in the *XT sequence* (+12.6% to -10.6% from mean) and these changes were well correlated with angle between diffusion gradient direction and positive slice encode axis ($r = -0.97$, $p < 0.001$, 60 directions, Fig. 3a). ADC from the *XT sequence* did not show any correlation with the other axes (read axis $r = -0.04$, $p = 0.77$; phase axis $r = -0.01$, $p = 0.91$). Furthermore, the ADC variations in *no_XT sequence*, which were an order of magnitude lower (+1.1% to -0.1% from mean), were still correlated only with the slice-encode axis ($r = -0.53$, $p < 0.001$, 60 directions, Fig. 3a).

The rotationally invariant MD from an ROI drawn on the phantom was $1.5949 \pm 0.0002 \times 10^{-3} \text{ mm}^2/\text{s}$ in the *no_XT*, and $1.5992 \pm 0.0003 \times 10^{-3} \text{ mm}^2/\text{s}$ in the *XT sequence* (Fig. 3b), an increase of 0.27%. Upon cross-term correction, MD from the *XT_corr1* reduced to $1.5948 \pm 0.0003 \times 10^{-3} \text{ mm}^2/\text{s}$ (Fig. 3b), which was essentially identical to the *no_XT sequence*. FA from the isotropic phantom, on the other hand, showed a substantially larger increase from 0.0546 ± 0.0001 in the *no_XT sequence* to 0.0996 ± 0.0001 in the *XT sequence* (Fig. 3c). Upon cross-term correction, the FA from the *XT_corr1* was 0.0573 ± 0.0001 (Fig. 3b). Histogram of the FA from an ROI drawn inside the isotropic phantom reflects the increase in FA in the *XT sequence* and the recovery after cross-term correction (Fig. 3d).

Chimpanzee Scan

DTI maps of the chimpanzee brain acquired with the *XT sequence* showed significant bias in eigenvectors in the GM regions compared to the *no_XT sequences* (Fig. 4, white arrows). This bias was removed upon cross-term correction using scripts written in Matlab. Tractography performed on the cortico-spinal tract, using a seed-mask in the cerebral peduncles, yielded a preferential tracking along the bias direction – diagonally across the image from the top-left to the bottom-right in the *XT sequence* (Fig. 5a). The number of pseudo-tracks crossing the midline at the corpus callosum was higher in the direction of bias (5.9% of total pseudo-tracks originating at an ROI drawn in the right-CP) compared to perpendicular to the direction of bias (1.5% of the total pseudo-tracks originating in the left-CP ROI) in the *XT sequence*. The ratio of the number of fibers along and perpendicular to the bias direction was 4.0 in the *XT sequence* compared to 0.7 in the *no_XT sequence*. This bias was eliminated by *XT_corr2* algorithm, and the ratio was restored to 0.8 albeit the percentage of pseudo-tracks crossing midline remained low at 2.1 and 1.7 along and perpendicular to the bias, respectively.

The MDs obtained from ROI drawn on the left- and right-IC, respectively, in chimpanzee brain were $0.728 \pm 0.002 \times 10^{-3} \text{ mm}^2/\text{s}$ and $0.722 \pm 0.001 \times 10^{-3} \text{ mm}^2/\text{s}$, from the *no_XT* sequence (Fig. 5b), but increased to $0.875 \pm 0.004 \times 10^{-3} \text{ mm}^2/\text{s}$ and $0.893 \pm 0.006 \times 10^{-3} \text{ mm}^2/\text{s}$ with *XT* sequence, an increase of 20.3% and 23.7%, respectively. MDs from left- and right- ICs were $0.786 \pm 0.004 \times 10^{-3} \text{ mm}^2/\text{s}$, and $0.793 \pm 0.005 \times 10^{-3} \text{ mm}^2/\text{s}$ after correction, which were 8% above and 9.8% above the MD obtained from the *no_XT* sequence. Similarly, FAs obtained using the *no_XT* sequence from the left and right IC in chimpanzee brain were 0.581 ± 0.003 and 0.593 ± 0.004 , respectively (Fig. 5c). The change in FA in the *no_XT* sequence depended on the orientation of the fiber, and was seen to increase to 0.597 ± 0.004 from the left IC and decrease to 0.547 ± 0.004 from the right IC respectively in the *XT* sequence, a change of +2.8% and -7.9%. FA obtained by *XT_corr1* was 0.556 ± 0.004 and 0.548 ± 0.005 in the left- and right-IC respectively, a change of -4.2 and -7.7% from the *no_XT* sequence. The ratio of FA in the left- to the right-IC was 0.98 in the *no_XT* sequence, 1.09 in the *XT* sequence and 1.01 after cross-term correction.

Discussion

Effects of gradient cross-terms were visualized as variation in signal in the DWI images of an isotropic phantom. These signal changes were well correlated with the angle between diffusion gradient and encoding axis, with large variations observed when the diffusion gradients were pointed along the encoding axis with most significant cross-terms. Artifacts due to cross-terms were visible in the DTI maps reconstructed from an isotropic phantom as well as from *in-vivo* brain as a bias in the principal eigenvector line-map or a tinge in the color-map. Gradient cross-terms caused an increase in MD in both isotropic and anisotropic samples. However, while FA increased across the entire isotropic sample, change in FA was dependent on the direction of the WM fiber tracts in chimpanzees, with fibers along the bias showing an increase, and perpendicular to the bias showing a slight decrease in anisotropy index. Finally, WM tractography performed with a seed mask in the left- and right-CP reflected this asymmetry with more fibers along the bias than against it.

The magnitude of the gradient cross-terms were determined using a calibration scan performed with diffusion gradients along the positive and negative read-, phase-, and slice-encoding axis. The b-matrix was corrected with these cross-term factors, and tensor reconstruction performed with the corrected b-matrix. The FA and MD values after correction more closely agreed with the values obtained from sequence without cross-terms, and the bias in principal eigenvectors disappeared. However, the tensor values did not completely recover, probably due to the small decrease in SNR due to the misplaced rephase-gradient.

Manifestation of cross-terms errors

The b-factor for signal attenuation in a DWI is the sum of contributions from the imaging gradients, diffusion gradients, and the gradient cross-terms between them. Gradient cross-terms, therefore, add to the signal attenuation in DWI, and increase the MD if unaccounted for during tensor calculations. Furthermore, the gradient cross-terms along each encoding axis depend on the magnitude and timings of the imaging and diffusion gradients. As the diffusion gradients are rotated in a DTI acquisition scheme and the diffusion gradient magnitude along each encoding direction changes, contribution of cross-term to each of the b-matrix elements also change. In the *XT* sequence, DWI signal from the isotropic phantom was lowest, and the ADC was largest, when the diffusion gradient was along the positive slice-encoding axis. This directional dependence of the DWI signal manifests as diffusion anisotropy, with an 82% increase in FA of the isotropic phantom and a strong bias in the principal eigenvector. Similar increase in FA and bias in principal eigenvectors were observed from low anisotropy regions of the chimpanzee brain *in-vivo*.

Asymmetric changes to anisotropy were observed from the white matter fibers in the *in-vivo* scans, with anisotropy of fibers pointing along the bias increased and those of fibers pointing perpendicular to the bias were slightly reduced. Detailed analysis was performed on a small segment of the cortico-spinal tract at the region of the IC, as these fibers were directed roughly perpendicular to the bias in the right side and roughly parallel to the bias on the left side of the chimpanzee brain. Indeed, asymmetric changes were clearly observed in this small segment of WM, and could potentially be visualized as an artificial lateralization of WM fibers in the brain. Furthermore, the bias in principal eigenvector was clearly visible in the GM in *in-vivo* scans of the chimpanzee brain (Fig.4), but not obvious in the WM. FSL based tract tracing algorithm detected significant asymmetries in the pseudo-fiber tracks originating from the cerebral peduncles in the *XT sequence*, that was absent in the *no_XT sequence*. The relative number of pseudo-fiber tracks detected originating in the right CP and crossing into the left hemisphere (along the bias) was about 4 times that originating in the left CP and crossing into the right hemisphere (perpendicular to the bias), and was thought to be a direct result of this bias.

While MD in the isotropic phantom increased only marginally, probably due to the uniform sampling of DWI around the slice encode axis, MD from IC in chimpanzee brain increased by around 20–24% in both the left- and right-ICs. The large changes in MD seen in anisotropic sample may be due to the relatively large changes to the off-diagonal components of the b-matrix, which need not be compensated by uniform sampling (9,15–17). MD from the anisotropic region was still elevated on cross-term corrections, and was ~8–10% higher in white matter parallel- and perpendicular-to the bias.

Gradient cross-term correction algorithms

Ideally, cross-term effects should be minimized during image acquisition. The most optimal way would be to allow complete rephasing of gradients before the application of new gradient set. However, this is often not practical and can result in very large TEs or low b-values. Routinely, pulse sequences apply imaging gradients (smaller moments), before the diffusion gradients are rephased, allowing the use of moderate to large b-values at reasonable TEs. This leads to gradient cross-terms of the order of 1% of the total b-value, which do not greatly affect the tensor calculation. However, there are increasing numbers of studies that use high resolution, high b-value imaging techniques that can have significant gradient cross-terms. High resolution DTI, for application in small animals, uses larger imaging gradients, thereby increasing the cross-terms. Recent advances in DTI sampling techniques to resolve crossing fiber issues such as high-angular resolution diffusion imaging (HARDI) and q-ball imaging use high b-values, and therefore increase the gradient interactions. Lastly, long diffusion time pulse sequences also increase the cross-terms due to the long evolution times. Customized pulse sequences written to realize these DTI need to derive the b-matrix carefully and accurately to remove artifacts due to cross-terms. If not, schemes to correct gradient cross-terms artifacts need to be used.

Cross-term correction schemes routinely used include geometric averaging of diffusion weighted images acquired with opposing diffusion gradient directions (7,10,18) and non-collinear sampling with diffusion gradients over the entire sphere (19,20). Both methods involve acquisition of additional diffusion gradient directions effectively doubling the scan time. Such correction must be performed with modified gradient schemes at the same time as the original acquisition and failure to complete the symmetric acquisition may yield residual artifacts. Furthermore, geometric averaging method for cross-term correction could yield similar errors due to noise (discussed in the next section). The method described herein involves performing a calibration scan on isotropic phantom with six diffusion directions, the cross-terms factors derived can be used to correct artifacts in all scans acquired on a post-hoc basis.

The most effective method for post-hoc correction would be to use a complete b-matrix derived as integral of moments of all gradients along each axis (3,4). This can be done within the pulse sequence at each time-interval, as in the Siemens DTI pulse sequence which calculates and outputs the b-matrix in its measurement data headers. However, this information can be lost during (the sometimes multiple) conversions of images into formats that can be read into the DTI processing package. Custom pulse-sequences may neglect to recalculate the b-matrix or make it available for processing during image conversion steps. Furthermore, DTI reconstruction packages often need the b-values to be specified in a one-dimensional vector. We chose to modify the b-matrix using the cross-terms factors derived from a calibration scan and pass the new b-matrix into the tensor calculation algorithm.

The gradient cross-term correction algorithms implemented herein corrected the increase in FA and MD, the bias in principal eigenvector from the isotropic phantom, as well as the bias in principal eigenvector seen in chimpanzee brain. The asymmetries seen in FA and MD were completely eliminated. It has been estimated that small errors in input b-values can have a strong effect on the MD, FA and fiber tracking results (21), and the ability to provide b-matrix as an input to the Matlab algorithm was directly responsible for accurate estimation of DTI parameters. However, FSL package provides a set of advanced tools for DTI processes including tract-tracing, allowing uniform processing of DTI. Indeed, the ratio of fibers traced along and perpendicular to the bias was 0.7 in the *no_XT sequence*, and greatly increased to 4.0 in the *XT sequence*, which returned to 0.8 in the corrected reconstruction.

Possible source of error in cross-term correction

It should be noted that the FA obtained after correction from WM (all directions) in chimpanzee brain was 5.9% below, and MD was 8.9% above those from the *no_XT sequence*. Furthermore, the total fraction of pseudo-tracks passing through the corpus callosum originating at the cerebral peduncles dropped from 15% in the *no_XT sequence* to 3.7% after FSL based correction was applied to the *XT sequence*. These discrepancies could be attributed to the errors in cross-term estimation due to noise in the calibration scan and the fact that acquisitions were done in separate sessions.

Noise in the images introduces error in the calculated DTI parameters as well as cross-term factors (1). The SNR of the b0 images were relatively high for the calibration scans, but that from the high b-value images were only 9.3 ± 1.1 . An error of $\pm 1\%$ in the signal obtained at high b-values could yield as much as a $\pm 6\%$ change in the calculated cross-term factors, propagating errors into the calculated DTI parameter maps. Cross-terms could therefore be calculated on average signal intensities obtained from an ROI drawn on the entire isotropic phantom except regions close to the edges. Indeed the cross-term factors in the slice encode direction varied between 121 s/mm^2 and 155 s/mm^2 within the various slices and repetitions due to noise, with an average of $136.8 \pm 1.6 \text{ s/mm}^2$. The phantom calibration can also be repeated multiple times and cross-terms obtained as an average to improve the accuracy.

Sequence modification

A standard double-spin echo sequence was modified by moving the rephase lobe of the slice-select gradient pulse from immediately after the 90° RF pulse to immediately before the EPI readout. The gradient so placed, caused large first order moment due to its persistence (for $\sim 75 \text{ ms}$), and the diffusion gradients applied between the slice select and rephase gradients cause significant gradient cross-terms. Slice-select gradient was chosen as the axis to introduce the cross-terms in the *XT sequence* as cross-term factors could be maximized by thin slice imaging, and the sequence could be achieved with no changes to the minimum required echo-time. The slice rephase gradient moment was 18 mT.ms/m compared to 3.4 and 3.3 mT.ms/m respectively for the readout and phase directions with 1.8

mm isotropic resolution chosen for imaging. A relatively large cross-term factor ($\sim 10\%$ of the total b-value) was achieved with this *XT sequence* and imaging protocols selected.

DTI phantom

The DTI phantom was made in-house from with 1 M mannitol + 0.1 M creatine in distilled water. Mannitol and creatine decreased the mean diffusivity of water (from $\sim 2.6 \times 10^{-3} \text{ mm}^2/\text{s}$ to $1.59 \times 10^{-3} \text{ mm}^2/\text{s}$) and increased the SNR of the DWI. The solute concentrations of this inexpensive isotropic phantom was optimized to provide sufficient signal from high b-value images, while at the same time to provide sufficient signal differences due to cross-terms alone, when the gradient direction was rotated in the calibration scans. The CNR was estimated at 6.7 this phantom, 3.9 for saline phantom, and 6.3 for a phantom with ADC of $0.7 \times 10^{-3} \text{ mm}^2/\text{s}$. While several examples of anisotropic phantoms exist in the literature (22,23), we chose to explore the effects of gradient cross-terms in *in-vivo* scans of chimpanzee brains.

Conclusion

Presence of large gradient cross-terms in a diffusion pulse sequence can cause errors in FA, MD, and eigenvectors in both isotropic and anisotropic regions, leading to erroneous fiber tracking and estimation of laterality. These artifacts can be corrected by first determining the cross-term factors using calibration scan on isotropic phantom and then modifying each element of the b-matrix with the cross-terms during DTI reconstruction. For customized sequences involving large b-values, high-resolution imaging, or long diffusion or echo times, evaluation of the effect of gradient cross-terms on an isotropic phantom and correction of their effects are recommended.

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Figure 1.

a. Double spin echo diffusion weighted imaging sequence was modified to induce gradient cross-terms. The slice refocusing gradient pulse (filled in grey) for the excitation RF pulse was moved from between slice encode and diffusion gradient pulses in the original sequence (*no_XT*), to play out along with the readout dephase pulse in the modified sequence (*XT*). The solid black filled gradients are diffusion gradients. b. Variation in DWI signal intensity as a percentage of B_0 signal intensity from an isotropic phantom as diffusion gradients are rotated (60 direction DTI scheme). The *XT* sequence shows significantly larger variation in ADC compared to the *no_XT* sequence.

Figure 2.

Demonstration of cross-term artifact in isotropic phantom. Color map of the first eigenvector modulated by FA, with line representation of the direction of the first eigenvector in (a) coronal and (b) axial planes from a small region (first column – regions in red) of an isotropic phantom. While the principal eigenvector points in random directions in maps of the isotropic phantom obtained from the *no_XT sequence* (second column), eigenvectors from the *XT sequence* shows a clear bias and points diagonally in a and vertically in b (third column). This bias in the principal eigenvectors is corrected by the cross-term correction performed using calibration scan (*XT_corr1*, fourth column).

Figure 3.

Influence of cross-terms on tensor parameters in isotropic phantom. (a) Diffusivity calculated from individual diffusion directions of a 60 direction DTI scan shows large variations well correlated with angle between the diffusion gradient direction and positive slice encode axis in the *XT* sequence, but not in the *noXT* sequence. (b) Rotationally invariant mean diffusivity (MD) and (c) fractional anisotropy (FA) in an isotropic phantom derived from the *no_XT* sequence, *XT* sequence, and corrected reconstruction using calibration scan (*XT_corr1*). MD and FA obtained from the *XT* sequence are significantly higher than that from the *no_XT* sequence, and this increase is eliminated by through cross-term correction algorithm (*XT_corr1*). (d) Histogram of FA from isotropic phantom shows a large and uniform shift in FA towards the right in the *XT* sequence compared to *no_XT* sequence, which is essentially recovered by the cross-term corrections algorithms implemented herein.

Figure 4.

Demonstration of cross-term artifacts in chimpanzee. a. Color map of the principal eigenvector modulated by FA, overlaid on line representation of the direction of the principal eigenvector obtained by the *no_XT* sequence (left), *XT* sequence (middle) and after correction (*XT_corr1*, right), shown here in two slices (top and bottom rows) from the right hemisphere of a chimpanzee brain. A clear bias is seen pointing diagonally in the top-left to bottom-right direction in grey matter regions in the *XT* sequence (white arrows in middle column), which is corrected using the cross-term correction algorithm. (Note that the *no_XT* and *XT* sequences were acquired in separate sittings, and therefore there is a slight mismatch in the coronal projections obtained using fslview, FMRIB, Oxford, UK).

Figure 5.

Influence of cross-terms in anisotropic regions. (a) Results of tractography performed on a chimpanzee brain using the *no_XT* sequence (first column), *XT* sequence (second column), and after correction in FSL (*XT_corr2*, third column), obtained with seed mask in the left (red-yellow) and right (blue-light blue) cerebral peduncles (visualized at a threshold of 500), overlaid on B0 anatomical images. Pseudo-tracks (fiber tracks counted by the software) can be seen crossing the midline at the corpus callosum from the right to left direction, along the bias but not in the opposite direction in the *XT* sequence. This preferential tracking is eliminated in the corrected sequence which provides tracking results similar to the *no_XT* sequence. (Note that the *no_XT* and *XT* sequences were acquired in separate sittings, and therefore there is a slight mismatch in the coronal projections obtained using fslview, FMRIB, Oxford, UK). (b) Mean diffusivity (MD) and (c) fractional anisotropy (FA) from ROIs drawn on the left and right internal capsule (IC) in the chimpanzee brain derived from the *no_XT* sequence, *XT* sequence, and cross-term corrected (*XT_corr1*).