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A Simple Noise Correction Scheme for Diffusional Kurtosis Imaging

G. Russell Glenn^{a,b,*}, Ali Tabesh^{a,c}, and Jens H. Jensen^{a,c}

^aCenter for Biomedical Imaging, Medical University of South Carolina, Charleston, South Carolina, USA

^bDepartment of Neurosciences, Medical University of South Carolina, Charleston, South Carolina, USA

^cDepartment of Radiology and Radiological Science, Medical University of South Carolina, Charleston, South Carolina, USA

Abstract

Purpose—Diffusional kurtosis imaging (DKI) is sensitive to the effects of signal noise due to strong diffusion weightings and higher order modeling of the diffusion weighted signal. A simple noise correction scheme is proposed to remove the majority of the noise bias in the estimated diffusional kurtosis.

Methods—Weighted linear least squares (WLLS) fitting together with a voxel-wise, subtraction-based noise correction from multiple, independent acquisitions are employed to reduce noise bias in DKI data. The method is validated in phantom experiments and demonstrated for in vivo human brain for DKI-derived parameter estimates.

Results—As long as the signal-to-noise ratio (SNR) for the most heavily diffusion weighted images is greater than 2.1, errors in phantom diffusional kurtosis estimates are found to be less than 5 percent with noise correction, but as high as 44 percent for uncorrected estimates. In human brain, noise correction is also shown to improve diffusional kurtosis estimates derived from measurements made with low SNR.

Conclusion—The proposed correction technique removes the majority of noise bias from diffusional kurtosis estimates in noisy phantom data and is applicable to DKI of human brain. Features of the method include computational simplicity and ease of integration into standard WLLS DKI post-processing algorithms.

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*Corresponding Author. G. Russell Glenn, BS, BA, Medical Scientist Training Program (MSTP-4), Center for Biomedical Imaging, Department of Neuroscience, 96 Jonathan Lucas Street, MSC 323, Charleston, SC 29425-0323, Tel: (843)580-2292, glennr@musc.edu.

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INTRODUCTION

The magnitude reconstruction typically used in MRI combines the real and imaginary components of a complex spatial signal so that the resulting image is independent of the arbitrary phase setting and is not affected by phase artifacts (1). However, this non-linear operation transforms the Gaussian (normal) distribution of random noise for the real and imaginary component images and thereby introduces a positive bias for the magnitude signal that is inversely related to the signal-to-noise ratio (SNR) (2,3).

For many MRI sequences, the SNR is sufficiently high so that this noise bias is negligible. However, several quantitative imaging techniques, such as diffusion, perfusion, and functional MRI, utilize echo-planar imaging (EPI), which has relatively poor SNR (4). For diffusion MRI, the SNR is further reduced by diffusion weighting of the signal (5). As a result, diffusion weighted images (DWIs) and diffusion parameters estimated from DWIs are particularly susceptible to the effects of noise (6). For example, noise bias may significantly alter estimates for both the mean diffusivity (MD) and fractional anisotropy, as conventionally obtained with diffusion tensor imaging (DTI) (6–9).

Diffusional kurtosis imaging (DKI) is an increasingly utilized diffusion MRI technique, which extends DTI by relaxing the assumption that the displacement of water via diffusion in biological tissue follows a Gaussian distribution (NB: the distribution of water displacements should not be confused with the noise distribution) (10,11). As a result, DKI includes the diffusional kurtosis in the DWI signal model through the 4th order cumulant expansion of the displacement distribution (10,11). In order to more accurately characterize the DWI signal from restricted diffusion that occurs in biological tissues (12), DKI employs a more complicated signal model that includes higher order terms in the b-value, which typically requires the use of larger maximum b-values (10,11,13). As a result, parameter estimation for DKI can be more sensitive to noise effects than for DTI (14–17), which limits the attainable resolution. Furthermore, certain regions of interest (ROIs) in the brain, such as the globus pallidus, have a relatively low SNR due to a high tissue iron concentration that shortens T2 (18). As a result, noise disproportionately affects diffusion parameter estimation in these regions. It may therefore be beneficial to implement a noise correction scheme that can remove the majority of noise bias from DKI data and thereby improve the accuracy of DKI-derived diffusion parameter estimates.

Noise correction is complicated by the fact that the variance of noise is not known a priori and must typically be estimated from characteristics of the reconstructed images (19–21). Two methods that have been used previously involve calculation of the mean or standard deviation of background noise level or calculation of the variance of the image intensity over a spatial ROI (19–25). Although the noise bias can theoretically be estimated by the mean or standard deviation of the background noise (19–21), this method is problematic for noise correction in DKI because EPI sequences are susceptible to image artifacts in the background region (26,27), which can lead to an overestimation of the noise bias. Measuring the variance of intensity values within a spatial ROI may also be unreliable, because a spatially homogeneous ROI may be difficult or impossible to find and intrinsic variability in the spatial signal also leads to an overestimation of the noise bias. As a result, voxel-wise

noise estimations from multiple, independent acquisition schemes are preferred over single acquisition methods (22,25). In addition, ROI-based noise estimates are not suitable for spatially varying noise distributions, as may result from the use of parallel imaging, which also requires the noise level to be estimated in a voxel-wise manner (28–31). Since parallel imaging is routinely used to decrease acquisition time, background noise estimators are almost never preferred to voxel-wise methods. The major drawbacks to multiple acquisition schemes are increased scan time and increased signal variance from non-thermodynamic factors such as patient motion or pulsatile changes.

There are a wide variety of noise correction methods available, including those that utilize lookup tables (3), global correction via a single noise correction term (19–21), non-linear maximum likelihood (ML) or maximum a posteriori (MAP) estimation which utilize Bessel functions in the measured signal model (12,25,32), nonlocal maximum likelihood estimation which sample neighboring voxels to determine spatially varying noise statistics (33,34), nonlinear diffusion filtering for spatially varying noise (35), spatially varying noise corrections involving confluent hypergeometric functions (36,37), and multistep weighting strategies to remove errors that can be introduced through the estimated weight factors (38). Although the more complicated noise correction techniques may have desirable theoretical properties under certain circumstances, they can be difficult to implement, require nonlinear optimization, and/or involve iterative fitting algorithms, which can be computationally demanding and may not guarantee a unique solution. DKI is well suited for linear estimation techniques because the system of equations can readily be linearized; however, ML estimation has also been applied to DKI data with spatially varying noise levels for robust parameter estimation (12). For a comprehensive discussion on the effects of different fitting strategies in diffusion MRI, the reader is directed to the work of Veraart et. al. (38,39).

The goal of this work is to describe a simple method for noise correction which is both straightforward to implement and removes the majority of the noise bias for DKI with low SNR. Our approach takes into account both the noise bias of the DWI signal, as well as the dependence of the noise variance on the signal magnitude that results from the Rician distribution (2,3,21). We consider a weighted linear least squares (WLLS) DKI analysis and propose a new set of weight factors to reduce the noise bias in the DKI parameter estimates. These weight terms account for the varying degrees of noise variance in the measured diffusion signal assuming the noise in each independent scan is well-described by a Rician distribution. The noise correction terms are calculated from a voxel-wise noise map estimated from multiple image averages, thereby accommodating for spatially varying noise (31). This noise correction scheme is compatible with well-established DKI analysis procedures (19). By preserving the linearity of the estimation problem, our approach guarantees a unique solution with minimal computational demands.

THEORY

Noise Correction in Diffusion MRI

We consider first the DKI signal model for an individual voxel:

$$S(\mathbf{g}) = S_0 e^{-bD(\mathbf{n}) + \frac{1}{6}b^2 D^2(\mathbf{n})K(\mathbf{n})}, \quad [1]$$

where $S(\mathbf{g})$ is the theoretical diffusion signal for a diffusion encoding gradient vector, $\mathbf{g}$, S_0 is the diffusion signal with no diffusion weighting, and $D(\mathbf{n})$ and $K(\mathbf{n})$ are the directional diffusivity and the diffusional kurtosis, respectively, along the normalized vector $\mathbf{n} = \mathbf{g} / \sqrt{b}$ (10,11). Here we have defined $\mathbf{g} = \sqrt{b}\mathbf{n}$, with b being the b-value which summarizes the effect of the diffusion weighting gradients on the diffusion signal, and $\mathbf{n}$ being the normalized diffusion encoding gradient direction.

The signal model in Eq. [1] describes the fourth-order cumulant expansion of the diffusion signal, which accounts for the leading effects of restricted, non-Gaussian diffusion on the diffusion MR signal, provided the b-value is not too large. However, in magnitude MR images, the measured signal is a biased estimator of the theoretical signal, and the expected value of the measured signal is always greater than the expected value of the theoretical signal (3). The difference between these two quantities is termed the noise bias.

If we consider Rician distributed noise and, for the moment, assume the noise variance, σ^2 , in the channels of the receive coil is known, then the expected value of the measured signal squared for arbitrary SNR is given by (2,19,20):

$$M^2 = S^2 + 2\sigma^2, \quad [2]$$

where the brackets denote the expected value of a random variable and M and S refer to the measured and theoretical signals, respectively.

Eq. [2] demonstrates a few key features of the effects of noise in magnitude MR images. First, noise adds in quadrature, and so in applying noise correction it is natural to consider the squares of the measured and ideal signals, sometimes termed power images (19). Second, the variance of noise, σ^2 , does not depend on the signal amplitude or the applied b-value. Nonetheless, the noise bias in the root mean square (RMS) measured signal estimator will depend on the signal amplitude because of the nonlinearity of Eq. [2], which is the source of systematic bias in diffusion parameter estimates taken from noisy DWIs. Consequently, for low b-value (high SNR) images the theoretical signal is typically sufficiently strong so that noise bias is negligible. However, for high b-value (low SNR) images, the noise bias accounts for a larger portion of the measured signal, and it becomes important to account for the effects of noise in the data analysis.

During a diffusion MR experiment, we acquire voxel-wise estimates for the measured signal in Eq. [2] over a pre-determined set of diffusion weighting gradient vectors. The expected value for the noise corrected signal squared for a given gradient vector can then be estimated by (19,20):

$$S_g^2 = M_g^2 - \eta^2, \quad [3]$$

where we have defined the noise parameter term, $\eta^2 = 2\sigma^2$, and the subscript $\mathbf{g}$ denotes the applied diffusion weighting gradient vector, $\mathbf{g}$. We have converted the variable $\mathbf{g}$ from a functional argument in Eq. [1] to a subscript in Eq. [3] to denote the transition from a continuous theoretical relationship to a discrete set of sample estimates acquired in a typical DKI scan.

Then, to estimate the diffusion parameters, we consider the equation:

$$\ln(S^2(\mathbf{g})) = 2 \left(\ln(S_0) - bD(\mathbf{n}) + \frac{1}{6}b^2D^2(\mathbf{n})K(\mathbf{n}) \right), \quad [4]$$

which follows directly from Eq. [1]. Note that this is linear in $D(\mathbf{n})$ and $D^2(\mathbf{n})K(\mathbf{n})$. By assuming in a diffusion experiment that $S_g^2 \approx S^2(\mathbf{g})$, one then sees that Eqs. [3] and [4] imply:

$$\ln(M_g^2 - \eta^2) \approx 2 \left(\ln(S_0) - bD(\mathbf{n}) + \frac{1}{6}b^2D^2(\mathbf{n})K(\mathbf{n}) \right), \quad [5]$$

which forms the basis for the least squares estimation problem. Because the variance of noise for the log-transformed squared signal estimates in Eq. [5] is not a constant, we perform a WLLS fit to find estimates for $D(\mathbf{n})$ and $D^2(\mathbf{n})K(\mathbf{n})$. The cost function for the WLLS estimation problem is then given by:

$$C \equiv \sum_{\mathbf{g} \in G} w_{\mathbf{g}} \cdot \left[\ln(M_{\mathbf{g}}^2 - \eta^2) - 2\alpha_{\mathbf{g}} \cdot \mathbf{x}_{\mathbf{g}}^T \right]^2 \Theta(M_{\mathbf{g}}^2 - \eta^2), \quad [6]$$

where G is the set of all gradient vectors used in an experiment, $w_{\mathbf{g}}$ is the weight factor for the given gradient vector, $\alpha_{\mathbf{g}} = [1, b, b^2]$ is a known vector defined by the experiment,

$\mathbf{x}_{\mathbf{g}} = [\ln(S_0), -D(\mathbf{n}), \frac{1}{6}D^2(\mathbf{n})K(\mathbf{n})]$ is the unknown vector of parameters to be estimated, and Θ is the Heaviside step function to zero out terms where the estimate for the expected value of the measured signal squared falls below the noise floor, $M_{\mathbf{g}}^2 < \eta^2$, which may occur in practice when estimating $M_{\mathbf{g}}^2$ from very noisy signals. The quantities $D(\mathbf{n})$ and $D^2(\mathbf{n})K(\mathbf{n})$ depend linearly on the diffusion and diffusional kurtosis tensor components (11,13), which are the ultimate parameters to be determined. However, the details of these tensor relationships are not needed for describing our noise correction scheme. We note that since $w_{\mathbf{g}}$ (defined in [7]) and $\Theta(\dots)$ are independent of $\mathbf{x}_{\mathbf{g}}$, the cost function in [6] is convex and therefore amenable to efficient numerical solution (see [9]).

The weight factors in Eq. [6] account for heteroscedasticity of the noise variance across log-transformed measurements. In general, there are two non-physiological factors that affect the variance of the measured diffusion signal; the Rician distribution of thermal noise in magnitude images, whose variance depends on the strength of the underlying signal (2,3), and the log transformation, which distorts the variance of the noise distribution (40).

By considering these two effects, the weight factors are found to be:

$$w_g = \frac{(M_g^2 - \eta^2)^2}{(M_g^2 - \frac{1}{2}\eta^2)}, \quad [7]$$

where the term in the numerator arises from the propagation of uncertainty in the squared signal following the log transformation (40), and the denominator arises from the magnitude-dependent variance of noise in the squared signal (18). A derivation of Eq. [7] is given in the appendix.

To minimize the difference between the noise corrected signal estimator and the assumed diffusion model over a full DKI dataset, we choose the set of diffusion parameters in the unknown vector, $\mathbf{x}^*$, to minimize the cost function in Eq. [6]. The solution to this problem can be accomplished with standard numerical procedures. For example, to solve it analytically, we let DT and KT be the second order diffusion and fourth order kurtosis tensors, respectively, as defined in (13), $MD = \text{tr}(DT)/3$, $V = MD^2 \cdot KT$,

$$h(\mathbf{g}) = [1, -b [n_1^2, n_2^2, n_3^2, 2n_1n_2, 2n_1n_3, 2n_2n_3], \frac{1}{6}b^2 [n_1^4, n_2^4, n_3^4, 4n_1^3n_2, 4n_1^3n_3, 4n_1n_2^3, \dots, 4n_1n_3^3, 4n_2^3n_3, 4n_2n_3^3, 6n_1^2n_2^2, 6n_1^2n_3^2, 6n_2^2n_3^2, 12n_1^2n_2n_3, 12n_1n_2^2n_3, 12n_1n_2n_3^2]], \quad [8]$$

be a known vector defined by the diffusion weighting vector, $\mathbf{g}$, $\mathbf{H} = 2[h(\mathbf{g}_0)^T, \dots, h(\mathbf{g}_j)^T]^T$, be the known design matrix defined by the DKI experiment over all the N_g applied diffusion weighting gradient vectors $\mathbf{g}_j$ ($j = 1, 2, \dots, N_g - 1$), $\mathbf{y} = [\ln(M_{g_0}^2 - \eta^2), \dots, \ln(M_{g_j}^2 - \eta^2)]^T$ be the vector of log-transformed corrected signals squared, $\mathbf{W} = \text{diag}([w_{g_0}, \dots, w_{g_j}])$ be the weight matrix calculated from Eq. [7], and $\Theta = \text{diag}([\Theta(M_{g_0}^2 - \eta^2), \dots, \Theta(M_{g_j}^2 - \eta^2)])$ be the Heaviside matrix. Then:

$$\mathbf{x}^* = (\mathbf{H}^T \mathbf{W} \Theta \mathbf{H})^{-1} \mathbf{H}^T \mathbf{W} \Theta \mathbf{y}, \quad [9]$$

is the unique solution to the WLLS estimation problem, where

$$\mathbf{x}^* = [\ln(S_0), DT_{1,1}, DT_{2,2}, DT_{3,3}, DT_{1,2}, DT_{1,3}, DT_{2,3}, \dots, V_{1,1,1,1}, V_{2,2,2,2}, V_{3,3,3,3}, V_{1,1,1,2}, V_{1,1,1,3}, V_{1,2,2,2}, V_{1,3,3,3}, \dots, V_{2,2,2,3}, V_{2,3,3,3}]$$

contains the distinct elements of the noise corrected diffusion and kurtosis tensors (13).

Voxel-Wise Estimation of the Noise Parameter

Noise correction is complicated by the fact that the variance of noise in the complex images, σ^2 , introduced in Eq. [2] is not known a priori and can vary spatially if parallel imaging is used (28–31). Consequently, estimation of σ^2 is a key problem in the analysis of noise.

To obtain voxel-wise estimates for σ^2 , we acquire a sequence of independent estimates for the diffusion signal over a set of gradient vectors, $(\hat{M}_{n,\mathbf{g}})_{n=1}^N$ for $N > 1$, where $\hat{M}_{n,\mathbf{g}}$ is the

estimate for the measured diffusion signal for the n^{th} sequential diffusion experiment for the gradient vector, $\mathbf{g}$. The expected values for the signal and squared signals are then given by:

$$M_{\mathbf{g}} = \frac{1}{N} \sum_{n=1}^N \hat{M}_{n,\mathbf{g}}, \quad [11]$$

and

$$M_{\mathbf{g}}^2 = \frac{1}{N} \sum_{n=1}^N \hat{M}_{n,\mathbf{g}}^2, \quad [12]$$

respectively. The voxel-wise variance estimate for a given diffusion weighting gradient vector is then calculated as:

$$\hat{\sigma}_{\mathbf{g}}^2 = \left(\frac{N}{N-1} \right) \left[M_{\mathbf{g}}^2 - M_{\mathbf{g}}^2 \right], \quad [13]$$

where Bessel's correction is used to correct the bias in the variance estimate at the expense of a higher mean squared error.

The accuracy of Eq. [13] for estimating the noise variance from Rician distributed data depends on the SNR of the underlying image (36), which depends on the applied b-value. Since DKI acquisitions typically sample multiple gradient directions at a single applied b-value we average voxel-wise variance estimates over all gradient directions for a given b-value:

$$\hat{\sigma}_b^2 = \frac{1}{N_b} \sum_{\mathbf{g} \in B} \hat{\sigma}_{\mathbf{g}}^2, \quad [14]$$

where B is the set of all gradient vectors with the b-value, b , and N_b is the total number of gradient vectors applied along that b-value. Averaging over all gradient vectors for a given voxel eliminates the need for averaging over spatially distributed ROIs. This naturally allows for the possibility of spatially varying noise, since the noise distribution being estimated is constant for a given image voxel. Gaussian smoothing is applied to the variance map, as obtained with Eq. [14], using the previously recommended full-width half max (FWHM) of 1.25 times the voxel dimension (13).

The choice of which b-value to use to estimate σ^2 depends on the nature of the image being analyzed. For example, if there are no sources of variability in the measured signal intensity other than thermal noise, such as in phantom or simulated data, then the lowest b-value should be used to maximize the accuracy of the variance estimator, and analytically exact corrections, such as the fixed point method proposed by Koay et. al. can be used to correct noise estimates from Rician distributed data (36). However, in human DWI datasets, minor motion artifacts and pulsatile flow lead to increased variance estimates from cerebrospinal fluid (CSF) and partial-volume effects in CSF-containing voxels due to the large differences in brain parenchyma and CSF T2 decay rates. Since increased diffusion weighting minimizes the effects of CSF contamination, a higher b-value is recommended to establish a

conservative variance parameter estimate in human data and minimize the influence of other sources of variability. Otherwise the noise correction term may overestimate the noise bias, and noise correction via Eq. [3] will overcompensate for the effects of noise. We note that at very low SNR, Eq. [14] is theoretically expected to underestimate the true noise variance, e.g. at $\hat{\sigma}_b^2 \approx 0.8\sigma^2$ (36). However, using this conservative estimate of the noise level is in agreement with the goals of this paper as it is expected to remove the majority of noise bias and it helps minimize the effects of other sources of variability in real diffusion MR data. This important consideration is discussed in more detail below.

METHODS

Phantom Experiments

A previously validated, isotropic dairy cream phantom (41) was scanned with a Siemens 3T TIM Trio MRI scanner using a single-shot diffusion-weighted EPI sequence using a twice-refocused spin echo (42) (Fig. 1). Phase and magnitude reconstructions were acquired for 16 independent data sets for averaging the real and imaginary component of the signal vector in the complex plane prior to magnitude reconstruction to establish a reference standard for noise correction. For each dataset, 14 flip angles of 90°, 75°, 60°, 45°, 30°, 20°, 15°, 10°, 8°, 6°, 4°, 2°, 1°, and 0° were selected to modify SNR, and 5 b-values of 0, 500, 1000, 1500, and 2000 s/mm² were applied in a single gradient direction orthogonal to the imaging plane to characterize the diffusion signal. Other acquisition parameters were TR = 2000 ms, TE = 107 ms, voxel dimensions = 3 × 3 × 3 mm³, matrix size × number of slices = 82 × 82 × 1, fat suppression off, raw filter on, parallel imaging off, bandwidth = 2345 Hz/Px, and coil = single channel Tx/Rx CP head coil.

Because the phantom is not affected by physiological noise, the noise correction term, η , was calculated in the lowest b-value image (i.e., b = 0), and noise corrected parameter estimates were calculated by minimizing the cost function of Eq. [6] along the applied gradient direction. Uncorrected results are calculated by setting $\eta = 0$, and fitting the diffusion model to the squared signal, which reduces to the conventional approach for WLLS fitting in the diffusion MRI literature (40).

To be consistent with published DKI post-processing methods, we applied Gaussian smoothing to the noise corrected RMS images obtained by combining Eqs. [3] and [12] using a smoothing kernel with FWHM of 1.25 times the voxel dimensions (13).

Human Experiments

A healthy volunteer was scanned with a Siemens 3T TIM Trio MRI using a vendor-supplied, single-shot diffusion-weighted EPI sequence using a twice-refocused spin echo (42), 3 b-values of 0, 1000, and 2000 s/mm², 10 independent b0 images, and 2 independent acquisitions along 30 diffusion encoding gradient directions for each b-value to characterize the directional diffusivity and diffusional kurtosis tensors. Acquisition parameters used were TR = 5300 ms, TE = 100 ms, voxel dimensions = 3 × 3 × 3 mm³, matrix size × number of slices = 74 × 74 × 40, fat suppression on, raw filter on, parallel imaging factor of 2,

bandwidth = 1351 Hz/Px, and a 32 channel head coil with adaptive combine mode. The total scan time for each, independent acquisition was 5 minutes and 39 seconds.

In order to obtain data with different SNR levels, datasets were acquired at flip angles of 90°, 15°, and 10°. Two independent datasets were acquired at each flip angle to allow for the calculation of voxel-wise variance maps.

In order to apply noise correction to a standard DKI dataset and to calculate the noise corrected diffusion and kurtosis tensors, the voxel-wise noise correction term was calculated in the highest b-value images (i.e., $b = 2000 \text{ s/mm}^2$), and Eq. [9] was adapted to our in-house software (43) using a previously published pre-processing technique, which applies Gaussian smoothing to all noise-corrected DWIs using a Gaussian smoothing kernel of 1.25 times the voxel dimensions prior to tensor fitting (13), which was performed with WLLS by Eq. [9], without using the constrained fitting option. Figure 2 summarizes the proposed method of noise correction in human DWI datasets. Uncorrected results are calculated by setting $\eta = 0$, and applying WLLS fitting to the squared signals, as for the phantom experiments.

Both qualitative and quantitative assessments were performed to evaluate the effects of noise and noise correction in human data. For quantitative assessment, an ROI was defined in the globus pallidus by a simple connected components analysis. Since the SNR in the globus pallidus is relatively low compared to other parts of the brain, this region is expected to be particularly sensitive to the effects of noise.

RESULTS

Phantom Data

Theoretical and experimental results for the variance parameter estimator in Eq. [14] are given in Fig. 3. The accuracy of the estimator depends on the SNR of the image in which it is measured, and hence on the amount of diffusion weighting applied. The accuracy of the estimator can be expressed explicitly in terms of SNR, and for SNR greater than 2, Eq. [12] is more than 80% accurate at estimating the noise variance (36). As a result, when the noise correction term is calculated in DWIs with an SNR of 2, noise correction can be expected to remove the majority of noise bias from measured signal estimates without any further modifications to the variance parameter estimator.

Data for all flip angles and all b-values before and after complex averaging are shown in Fig. 4. The noise floor, η , dampens signal attenuation caused by diffusion for low SNR DWIs, which adversely affects diffusion parameter estimates at low SNR. Complex averaging preserves the shape of the diffusion signal curve well below the original noise floor and thus serves as a reference method for noise correction.

Signal characteristics of the phantom, shown in Fig. 5, show excellent agreement with assumed theoretical models.

Results from noise correction in phantom estimates of directional diffusivity and kurtosis are given in Fig. 6. Decreasing the flip angle reduced the SNR from 8.8 to 1.8, which decreased

the directional diffusivity estimate and increased the directional kurtosis estimate in uncorrected data. Noise correction improves the accuracy of parameter estimation of both directional diffusivity and directional kurtosis to within 5% error when compared to reference estimates for all SNRs greater than 2.1. The mean directional diffusivity and kurtosis were measured to be $1.06 \pm 0.03 \mu\text{m}^2/\text{ms}$ and $1.26 (\pm 0.03)$, respectively, which are in agreement with the values found by Fieremans et al. (41).

Human Data

Qualitative results for human data are depicted in Fig. 7 for a transverse slice taken at the level of the globus pallidus in a healthy volunteer. MD and mean kurtosis (MK) estimates are calculated from the full diffusion and kurtosis tensors. In general, MD is less affected than MK by the effects of noise bias, and MK tends to increase as SNR decreases.

Parameter estimates for the human data are qualitatively similar to those observed for the phantom data. Quantitative human results are displayed in Fig. 8. Changing the flip angle from 90° to 15° to 10° reduces the SNR in the globus pallidus from 3.9 to 2.0 to 1.8 in the $b = 2000 \text{ s/mm}^2$ images, respectively, which increased mean kurtosis estimates from $0.89(\pm 0.15)$ to $1.17(\pm 0.14)$ $1.44(\pm 0.19)$, with a total percent change of 62%. Noise correction reduced the respective parameter estimates to $0.79(\pm 0.16)$, $0.84(\pm 0.14)$, and $0.99(\pm 0.16)$ with a total percent change of 25%.

DISCUSSION

Our noise correction scheme for DKI has been demonstrated to significantly improve diffusion parameter estimates in phantom data with low SNR. The proposed method is also applicable in human data with low SNR. Features of our approach include mathematical simplicity of the equations, which permits linearization of the estimation problem, novel weight factors for the linear least squares fitting, ease of implementation and adaptability into standard software packages, and generation of voxel-wise noise correction terms which can accommodate spatially varying noise.

A limitation of our technique for estimating the noise level is that it assumes a Rician noise distribution, so care should be taken in the acquisition and reconstruction to ensure the Rician distribution of noise is preserved prior to estimation of the noise level. Common reconstruction steps that result in non-Rician noise include multi-channel acquisitions with the sum-of-squares coil combine algorithm, which results in the noncentral χ distribution, and application image processing filters prior to noise variance estimation, which can result in specific or unknown effects on the data distribution. For a detailed discussion of the effects of image reconstruction on the data distribution, the reader is directed to the work of Dietrich et al. (44). In addition, our technique for estimating the noise level requires at least two, independent acquisitions which increases the total scan time.

The accuracy and precision of the signal characteristics of the phantom compared to theoretical models is remarkable (see Fig. 3 and 5), which supports the validity of this phantom for the investigation of noise effects diffusion MRI. Furthermore, the agreement between the noise correction obtained by minimizing Eq. [6] and by applying complex

averaging is excellent (see Fig. 6), considering that these are two computationally distinct ways of correcting for the noise bias. Thus, the phantom results demonstrate the effects of noise and the efficacy of the proposed correction scheme in diffusion MRI data, in the ideal case where the signal characteristics are well known. However, there is a moderate dip in the mean directional kurtosis estimates in our noise corrected phantom data relative to the results from complex averaging at $\text{SNR} = 2$, which does not occur when non-linear, ML estimation is used (data not shown). This indicates that the proposed noise correction method is over-compensating for the effects of noise at this SNR level, although the exact origin of this is unclear.

In human data, there is little difference between the noise corrected and uncorrected parameter results for the 90° flip angle datasets. However, the effects of noise on the MK estimates in the globus pallidus can be seen for lower SNR images, and noise correction seems to remove the majority of the noise bias when compared to the 90° flip angle scans. As a result, noise correction may not be necessary for standard DKI datasets of the human brain, but may need to be considered if higher b-values, higher resolution, or accelerated acquisitions are desired, as these can decrease SNR. In addition, noise correction may be advantageous in DKI applications in the body, such as in the prostate, where SNR is low (17). It should also be pointed out that the SNR in the images taken with 15° and 10° flip angles fall slightly below the SNR threshold of 2.1 indicated by the phantom experiments. Thus, for these flip angles, the globus pallidus signal is sufficiently noisy that it becomes difficult to extract the meaningful signal from noise. Furthermore, in the noise maps demonstrated in Fig. 2, some physiological effects of noise are still apparent. For example, even at the highest b-value image some remaining CSF-contamination effects could be present which result in outliers in the measured variance image. In future studies, it may be useful to include outlier detection prior to Gaussian smoothing to decrease these effects in the noise map, but care should be taken to ensure that voxel-wise estimation is preserved. This was not explored here because the primary emphasis of this study was the phantom experiment, and the verification of a simple noise correction technique for DKI data.

Because the variance of the Rician distribution does not precisely equal the variance of noise in the real and imaginary images, others have recommended the use of an SNR-dependent function to correct the noise parameter estimation (36,37). Although this method creates a theoretically accurate estimator, it assumes that the image variance is solely due to random, thermal noise in the acquired signal. However, in human data with a multiple acquisition scheme, there are several other sources of variability in the image intensity values, such as bulk motion, pulsatile flow, and CSF contamination which tend to increase the estimation of the noise bias and overcompensate for the effects of noise on the diffusion parameter estimates. As a result, in human data, we recommend choosing a conservative estimate for the noise parameter, which may be derived from the highest b-value images. In Fig. 3, it is shown that at an SNR of 2, the variance estimator given by Eq. [13] is approximately 80% accurate. So even with no other sources of variability, this method is still expected to remove the majority of the non-physiological noise bias. Although physiological noise is suppressed by diffusion weighting, it is also affected by the signal strength (45). Thus, physiological noise may provide small contributions to the differences seen between noise maps derived from the 90° , 15° , and 10° flip angle scans in Fig. 7. However, we expect the

effects of physiological noise to be small at $b = 2000 \text{ s/mm}^2$, so differences in the noise maps arise from the SNR-dependence of our variance estimator.

Estimation of the noise level with Eq. [14] averages variance estimates for each voxel across multiple diffusion encoding gradient directions with a fixed b -value. In general, these estimates are taken from voxels with anisotropic diffusion profiles, where the SNR varies intrinsically for each direction. From Fig. 3, Eq. [13] is greater than 93% accurate when the SNR is greater than 3 and greater than 98% for SNR greater than 5. So, as long as the SNR remains above 3 across all gradient directions, anisotropy should have limited effects on the accuracy of the mean variance estimator. However, from SNR values between 3 and 1, the accuracy of Eq. [13] drops from 93% to 60%. So, for images with SNR between 1 and 3, the accuracy of the variance estimator can be reduced, particularly if there are a large number of directions with very low SNR. Because of the non-linearity of the relationship between SNR and the accuracy of the variance estimator (36), anisotropy can decrease the accuracy of Eq. [14] below what would be predicted from the average SNR across all directions. Thus, care should be taken in applying Eq. [14] to very noisy DWIs with SNR values that fall below 2. However, effects of anisotropy on noise estimation are not apparent in the in-vivo noise maps calculated from the 10° flip angle scan where the average SNR throughout the brain parenchyma is 3.3.

Since the variance of experimental inputs for Eq. [6] depend on the signal intensity, WLLS fitting is needed to solve the least squares minimization problem for the cost function C . However, WLLS fitting is complicated by the fact that the ideal weight factors, which are a function of the true signals, are unknown, and improper use of weighting strategies can have negative effects on parameter estimation (39). Thus accurately estimating the expected value of the measured signal squared, M_g^2 is crucial for WLLS fitting. In phantom experiments, where scan time and motion artifacts are not a major concern, this can be accomplished by increasing the number of independent image acquisitions for Eq. [12]. However, in acquiring human data, this is rarely practical. Thus, applying smoothing filters, such as Gaussian smoothing, to improve estimates of M_g^2 is recommended. Gaussian smoothing is a common feature of the DKI processing pipeline and is included in our in-house software package (13,43). An alternative method to address this problem, which has been recently proposed, involves first performing a linear least squares fit to estimate M_g^2 , which is then used to generate the weight factors for the WLLS fit (38). Without applying these corrections additional bias can be introduced from WLLS fitting of the log-transformed data.

CONCLUSION

Noise affects the measured signal in magnitude reconstructed diffusion MR images, which can lead to significant inaccuracies in diffusion parameter estimation from low SNR images. The effects of noise are greater in estimation of the diffusional kurtosis compared to the diffusivity in both phantom and human data. The noise correction scheme based on minimizing the cost function of Eq. [6] substantially reduces the noise bias in DKI parameter estimates. This method is particularly relevant for high resolution DKI acquisitions or for DKI studies that involve regions where the SNR is inherently poor.

APPENDIX

Derivation of the proposed weight factors

Linear least squares fitting assumes that errors in all measurements are uncorrelated and have an equal variance. When the variance of data points in the fitted model is known to differ, calculation of the best linear unbiased estimator requires each data point to be weighted by its relative precision. Therefore, standard WLLS dictates that the weight factors, w_i , for a cost function:

$$C \equiv \sum_i w_i \cdot F^2(Y_i), \quad [15]$$

where Y_i corresponds to the i^{th} measurement and $F(Y_i)$ is an arbitrary function, be given by:

$$w_i = \frac{1}{\text{var}[F(Y_i)]}, \quad [16]$$

with $\text{var}[F(Y_i)]$ being the variance for $F(Y_i)$. Since it is assumed that the measurement noise is uncorrelated, analysis of the propagation of uncertainty yields:

$$\text{var}[F(Y_i)] = \text{var}(Y_i) \left(\frac{\partial F}{\partial Y_i} \right)^2. \quad [17]$$

Thus:

$$w_i = \frac{1}{\text{var}(Y_i)} \cdot \left(\frac{\partial F}{\partial Y_i} \right)^{-2}. \quad [18]$$

In applying this general result to Eq. [6], we have $F(Y_i) = \ln(Y_i) - X_i$, where the random variable Y_i represents the theoretical signal squared, $S^2(\mathbf{g})$, and X_i is a noise-independent constant. Since (21):

$$\text{Var}(Y_i) = \text{Var}(S^2(\mathbf{g})) = 4\sigma^2 (S^2(\mathbf{g}) + \sigma^2), \quad [19]$$

and we have defined $\eta^2 = 2\sigma^2$ and estimated $S^2(\mathbf{g}) \approx M_{\mathbf{g}}^2 - \eta^2$ in Eq. [3], we have:

$$\text{var}(Y_i) = 2\eta^2 \left(M_{\mathbf{g}}^2 - \frac{1}{2}\eta^2 \right). \quad [20]$$

Since:

$$\left(\frac{\partial F}{\partial Y_i} \right)^{-2} = Y_i^2 = (M_{\mathbf{g}}^2 - \eta^2)^2, \quad [21]$$

We arrive at:

$$w_i = \frac{(M_g^2 - \eta^2)^2}{\left(M_g^2 - \frac{1}{2}\eta^2\right)}, \quad [22]$$

by substituting Eqs. [20] and [21] into Eq. [18], where an irrelevant factor of $2\eta^2$ has been discarded from the cost function.

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Fig 1.

Isotropic dairy cream phantom. **A:** Food grade heavy whipping cream was prepared by the method described by Fiermans et. al. (38) and placed into a cylindrical MR-transparent container. **B:** Coronal DWI acquisition of the phantom demonstrates two distinct fat and water signals when fat suppression is turned off. The intersection forms the cream signal which has an increased T2-weighted signal and mimics the properties of the diffusion signal in the human brain. The homogeneous cream ROI used in all phantom experiments is shown in white. The cream ROI contains $n = 138$ image voxels.

Fig. 2.

Noise correction scheme in human DKI datasets. **A:** Estimation of the noise level is done in the highest b-value images, and a minimum of 2 independent acquisitions are used to estimate the mean and RMS images given by Eq. [11] and the square root of Eq. [12] respectively (arrow a). **B:** The RMS and mean images are estimated and combined for each diffusion encoding direction in the highest b-value image to create a separate variance map for each gradient vector by Eq. [13] (arrow b). **C:** The independent variance maps are converted into a mean variance map by averaging the variance maps from each gradient direction at a given b-value by Eq. [14] (arrow c1). A smooth variance map is then created by Gaussian smoothing (arrow c2) and the noise map is generated (arrow c3). Noise correction is then applied to all RMS images in the DKI data set using Eq. [3] (arrow c4). **D:** The noise corrected DKI dataset is then processed using the in-house software, which includes Gaussian smoothing and the WLS fit given by Eq. [9] (arrow d) to calculate tensor-derived parameter estimates. **E:** Noise corrected parameter maps help reduce the effects of noise.

Fig 3.

Noise variance parameter estimation by Eq. [14]. **A:** Simulated image variance in Rician distributed data where the expected signal is calculated by Eq. [1], and the variance parameter σ^2 is set to 100. The image variance for the lowest b-value provides the most accurate estimate and the highest b-value provides the most conservative estimate for all flip angles. **B:** Experimental data from the phantom agrees with theoretical calculations. **C:** The accuracy of Eq. [13] can be expressed explicitly in terms of the SNR of the image used for its calculation. For $\text{SNR} > 2$ the variance estimator is greater than 80% accurate. The SNR dependence of the variance estimator is discussed in more detail in Koay et. al (36).

Fig 4.

Mean phantom cream ROI signal vs b-value for all 14 flip angles demonstrates the effects of the noise floor, η (dashed black line) in the uncorrected signal (blue) and the signal after complex averaging of 16 independent scans (red). The noise floor dampens the b-value attenuation of the diffusion signal in uncorrected images at low SNR resulting in significant inaccuracies in diffusion parameter estimates. Complex averaging allows for arbitrarily high SNR in phantom MR data, which diminishes the effects of the rectified noise floor and allows for a reference standard of diffusion parameter estimates.

Fig. 5.

The isotropic dairy cream phantom has well-defined signal characteristics. In all plots blue circles represent experimental data and the red lines represent fit curves to the assumed theoretical model. **A:** Noise histogram was taken from image voxels of all 16 b0 (i.e., b-value = 0) scans where the flip angle was set to 0° and fit to the Rice distribution with the true underlying signal equal to 0. **B:** The mean signal value of the Rice distribution with the signal equal to zero demonstrates the rectified noise floor and is directly proportional to the standard deviation of Gaussian noise in the real and imaginary channels. Consequently, complex averaging decreases the expected value of noise by a factor of $1/\sqrt{n}$, where n is the number of complex averages. By directly removing the noise bias, complex averaging serves as a reference standard for noise correction in phantom data. **C:** The 90° flip angle b0 image has a relatively high SNR and therefore a relatively low noise bias. As a result, complex averaging does not affect the mean signal value in the cream ROI. **D:** Phantom images for all b-values for selected flip angles demonstrate the experimental design. **E:** Signal strength in an MRI experiment is directly proportional to the projection of the magnetization vector into the transverse imaging plane. Changing the flip angle in the phantom scans allows us to experimentally modify the SNR of the diffusion experiment to test the effects of noise. **F:** The cumulant-expansion DKI signal model, Eq. [1], accurately characterizes the MRI signal dependence on b-value in phantom data and allows for the description of restricted diffusion of water in biological tissue.

Fig. 6.

Noise correction in phantom data improves the accuracy of parameter estimate to within 5% error for $\text{SNR} > 2.1$ when compared to the reference standard of complex averaging for noise bias removal. In both plots, the blue line represents the mean parameter estimates in uncorrected data, the red line represents the mean parameter estimates following noise correction, and the gray dashed line indicates $\pm 5\%$ error. Directional diffusivity and kurtosis are averaged over $n = 138$ isotropic voxels in the phantom cream ROI to calculate the mean diffusion parameter estimates.

Fig. 7.

Qualitative results from noise correction in human data. Changing the flip angle is used to modify the signal magnitude in diffusion MR data which affects SNR. MD shows no qualitative change by modifying SNR or after noise correction. MK shows qualitative enhancement around the globus pallidus with decreased SNR, which is decreased by noise correction. Noise maps are defined by the method described in Fig. 4. The color bar for the diffusivity is calibrated in units of $\mu\text{m}^2/\text{ms}$, while the bar for the kurtosis has a dimensionless scale. The bars for the b0 and noise maps use identical, arbitrary signal intensity scales.

Fig. 8.

Quantitative results before and after noise correction in the globus pallidus. **A:** Globus pallidus ROI with $n = 99$ voxels was defined using a simple, three dimensional connected components analysis in the brain, which is highlighted in yellow for a single transverse brain slice. **B:** MD estimates show small quantitative changes as a result of changing SNR or applying noise correction. **C:** MK estimates increase as SNR decreases due to noise bias, and noise correction improves the accuracy of mean kurtosis estimates from low SNR images compared to the estimates from images with the highest SNR. Error bars represent the standard deviation of the parameter estimate in the ROI. For both plots, error bars represent the standard deviation of parameter estimates in the ROI and the grey dashed line is the noise corrected parameter estimate from the 90° flip angle scan for reference.