Published in final edited form as:

Magn Reson Imaging. 2014 December ; 32(10): 1335–1343. doi:10.1016/j.mri.2014.07.004.

Phase-Aligned Multiple Spin-Echo Averaging: A Simple Way to Improve Signal-to-Noise Ratio of *in vivo* Mouse Spinal Cord Diffusion Tensor Image

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Abstract

Purpose—To improve signal-noise-ratio of *in vivo* mouse spinal cord diffusion tensor imaging using phase aligned multiple spin-echo technique.

Material and Methods—*In vivo* mouse spinal cord diffusion tensor imaging maps generated by multiple spin-echo and conventional spin-echo diffusion weighting were examined to demonstrate the efficacy of multiple spin-echo diffusion sequence to improve image quality and throughput. Effects of signal averaging using complex, magnitude and phased images from multiple spin-echo diffusion weighting were also assessed. Bayesian probability theory was used to generate phased images by moving the coherent signals to the real channel to eliminate the effect of phase variation between echoes while preserving the Gaussian noise distribution. Signal averaging of phased multiple spin-echo images potentially solves both the phase incoherence problem and the bias of the elevated Rician noise distribution in magnitude image. The proposed signal averaging with Bayesian phase-aligned multiple spin-echo images approach was compared to the conventional spin-echo data acquired with doubling the scan time. The diffusion tensor imaging parameters were compared in the mouse contusion spinal cord injury. Significance level (p-value) and effect size (Cohen's d) were reported between the control and contused spinal cord to inspect the sensitivity of each approach in detecting white matter pathology.

Results—Compared to the spin-echo image, the signal-noise-ratio increased to 1.84-fold using the phased image averaging and to 1.30-fold using magnitude image averaging in the spinal cord white matter. Multiple spin-echo phased image averaging showed improved image quality of the

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mouse spinal cord among the tested methods. Diffusion tensor imaging metrics obtained from multiple spin-echo phased images using three echoes and two averages closely agreed with those derived by spin-echo magnitude data with four averages (two times more in acquisition time). The phased image averaging correctly reflected pathological features in contusion spinal cord injury.

Conclusion—Our *in vivo* imaging results indicate that averaging the phased multiple spin-echo images yields an 80% signal-noise-ratio increase over the spin-echo images and a 40% gain over the magnitude averaged multiple spin-echo images with equal acquisition time. Current results from the animal model of spinal cord injury suggest that the phased multiple spin-echo images could be used to improve signal-noise-ratio.

Keywords

Bayesian phasing analysis; multiple spin-echo; DTI; spinal cord

1. Introduction

Quantitative diffusion tensor magnetic resonance imaging (DTI) has been widely applied as a tool for neuroscience research. For high-resolution imaging of the rodent central nervous system (CNS), diffusion MRI using a conventional Stejskal-Tanner spin-echo (SE) sequence remains one of the best approaches owing to its unrivaled image quality and ease of use. SE DTI has been used to generate high resolution images *in vivo* to avoid the partial volume effect and clearly delineate microstructural changes in the rodent spinal cord (1–3). Nevertheless, SE imaging is hindered by long acquisition time which limits the throughput and risks physiological rundown resulting in inaccurate diffusion coefficient measurements (4).

Echo planar imaging (EPI) is an ultra-fast imaging sequence, using a gradient echo train to acquire images in a fraction of a second (5,6). Despite recent reports in rodent spinal cord DTI using EPI diffusion weighted sequence (7–11), it remains a challenge to apply EPI to acquire high-quality mouse spinal cord DTI due to the susceptibility differences of air, bone and tissue, and through-plane dephasing from thoracic cavity (8,12,13). To minimize these susceptibility effects, multiple-shot EPI diffusion weighted sequence may be necessary. However, this elongates the acquisition time and significantly reduces the benefit of using EPI based measurements. Alternatively, fast-spin-echo (FSE) imaging retains the high image quality of the SE techniques while significantly shortening acquisition time through the acquisition of multiple echoes to cover phase encoding steps (14,15). The drawbacks of FSE imaging are image blurring and ghosting artifacts that originate from amplitude and phase modulations of the FSE k-space data (4,16,17). Additionally, when diffusion gradients are applied during a FSE sequence, phase variation along the phase-encoded direction can become more complicated, impeding accurate image reconstruction (15,18,19).

Compared to a conventional SE sequence, diffusion weighted multiple spin-echo (MSE) imaging variations have been shown to offer improved signal-to-noise ratio (SNR) by averaging the extra echoes within a k-space line (20–22). The advantage of this scheme is that it maximizes the signal averaging in each phase encoding step and avoids phase changes caused by phase-encoding gradients between echoes. This approach is expected to improve

SNR and could be used to provide additional option for T_2 estimation from a series of SE trains (22). Although MSE imaging is practically easy to implement obtaining high quality images, the SNR gain through averaging magnitude images remains less than optimal. To further improve the quality of MSE results, a better approach to average the acquired multiple echoes is needed.

Signal averaging of complex data theoretically maximizes the SNR of MSE acquisitions, but in practice, the phase variations caused by motion, hardware imperfections and field inhomogeneity often result in significant signal degradation averaging multiple echoes (23–25). Using absolute-value images, i.e. magnitude images, for averaging multiple-echo images avoids the image-to-image phase variation; in a numerical study by Nana et al. (22), a three-echo MSE image could achieve a 1.36-fold SNR of the single-echo imaging in the white matter (WM) region ($T_2 = 80$ ms, echo spacing = 24 ms). However, in averaging multiple magnitude images the Rician noise distribution induces skewedness with a non-zero offset of the mean (26–28). This offset results in raising the measured pixel intensity and limiting the SNR gained through averaging. Although a non-zero mean noise distribution has negligible effect at high SNR, it can bias measurements at low SNR, a critical issue in diffusion-weighted images and the resulting diffusion tensor calculations (26,28–30).

Appropriately phasing the complex MSE data prior to averaging allows the full realization of theoretical SNR gain of multiple echoes while eliminating phase artifacts (31,32), also known as the absorption-mode image, phase-aligned image, or simply phased image. Herein, we demonstrate the advantage of averaging phased MSE data using Bayesian probability theory. It eliminates phase artifacts, the noise correlations from averaging magnitude MSE images, and improves SNR achieving nearly $\sqrt{2}$ -fold of the conventional MSE magnitude images. To demonstrate this method's advantage, we compared the image quality and sensitivity between the SE and MSE imaging of the neuropathology in mouse model of contusion spinal cord injury (SCI).

2. Materials and Methods

2.1. Multiple Spin-Echo Data Acquisition

A conventional Stejskal-Tanner diffusion-weighted sequence was modified to acquire MSE by a variable-echo-spacing Carr–Purcell–Meiboom–Gill (CPMG) train of 180° pulses (Fig. 1). Inter-echo spacing (ΔTE) was minimized in order to maximize the signals of multiple echoes. The suppression of secondary echoes by crusher gradients was crucial due to the violation of the CPMG condition (33). Modified Shinnar-Le Roux refocusing pulses were used to compensate pulse imperfection (34). All experiments were conducted on an Agilent 4.7 T imaging system (Agilent Technologies, Santa Clara, CA, United States).

2.2. Phased Image Generation and Relative SNR Analysis

Phased images were generated using Bayesian probability theory to independently estimate the phase of each echo from the echo chain. The complete theory of this approach has been reported previously (31,32) and is given in the appendix. In brief, given the prior probability

of noise standard deviation, σ , the data, D , and the background information, I , the posterior probability for the phase, $P(\theta|\sigma DI)$, is used to estimate the phase, θ . Once the pixel-wise phase is estimated, the coherent signals are moved entirely to the real channel by:

$$S_{pi} = S_i \exp\{-i\hat{\theta}\}, \quad (1)$$

where S_i is the original i th voxel signal, S_{pi} is the i th voxel signal after phasing, and $\hat{\theta}$ is the estimated phase. After a successful phasing analysis, the imaginary channel contains only noise. The real channel containing totally coherent signals free of phase complications was computed independently for each echo (31). The imaginary channel data was not used in averaging thus only noise in the real channel was included in the averaged signal. The real channel noise level remains unchanged because each complex voxel was multiplied by $\exp\{-i\hat{\theta}\}$, a rotation that does not change the magnitude of a vector. Therefore, SNR of the MSE phased image is increased by $\sqrt{2}$ compared to that of the MSE magnitude image. The phased diffusion weighted images were then averaged for least-squares fitting to derive the diffusion tensor parameters. Three eigenvalues ($\lambda_1, \lambda_2, \lambda_3$) were calculated from the diffusion tensor matrix. The eigenvalue-derived parameters, including the relative anisotropy (RA), mean diffusivity (MD), axial diffusivity ($\lambda_{||}$), and radial diffusivity ($\lambda_{\perp}$), were calculated as previously reported (1,35,36). The phasing analysis was processed by the Bayesian Analysis of Common NMR Problems software developed at the Washington University by Dr. G. Larry Bretthorst (37).

The MSE signals were compared between complex data averaging (MSE-Complex), magnitude image averaging (MSE-Magnitude), or phased image averaging (MSE-Phased). To determine the theoretical SNR increase in the magnitude averaged MSE dataset, the ratio of the SNR of the averaged echo to the first echo was calculated according to:

$$\frac{SNR_{MSE}}{SNR_{echo1}} = \sqrt{\sum_{i=1}^N \left(e^{-\frac{\Delta TE_i}{T_2}} \right)^2}, \quad (2)$$

where T_2 values for cerebrospinal fluid (CSF), gray matter (GM), and WM were assumed to be 2000 ms, 100 ms and 80 ms, respectively (22).

2.3. Spinal cord injury and in vivo DTI

All surgical preparations, pre-, and post-surgery care were provided in accordance with the Public Health Service Policy on Humane Care and Use of Laboratory Animals, Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources, National Research Council, 1996), and with the approval of the Washington University Animal Studies Committee.

Five female C57BL/6 mice (Harlan Laboratories, Indianapolis, IN) weighing 18 – 22 g were given severe contusion SCI by a modified Ohio State University impactor after dorsal laminectomy at the T9 vertebral level (displacement: 1.0mm, velocity: 0.2m/s) (1,38). Another five sham-operated animals (uninjured) underwent a laminectomy without contusion and served as the control. The surgical site was closed in layers with 4-0 vicryl and nylon sutures. Injections of enrofloxacin (2.5 mg/kg) and lactated ringers (1.5 ml) were

given subcutaneously. Manual bladder expression of the injured mice was performed twice daily throughout the duration of the study (39). Softened rodent chow was provided. Body weights were measured and compared daily with the preoperative weight. High-calorie nutrient paste (Nutrical; Evsco Inc., Buena, NJ) was given to the mice to maintain body weights at 90% of their preoperative values. All injured mice showed complete paralysis with no ankle movement at 24 hours after injury.

All mice underwent in vivo spinal cord DTI at seven days after surgery. Mice were anesthetized with a mixture of 4.5 % isoflurane/O₂, immobilized in a custom MR-compatible immobilization device, and placed on a pad of circulating warm water. Anesthesia was maintained at 1.0 – 1.5 % isoflurane/O₂ and body temperature was maintained at 37°C throughout the DTI examination. An actively decoupled half-saddle surface coil (15 mm × 8 mm) covering vertebral segments T6 – T12 was employed as the receiver (40). The mouse was positioned inside of a 9 cm (inner diameter) actively decoupled Helmholtz transmit coil. The entire preparation was placed in the 4.7 T magnet equipped with a 15-cm (inner diameter) actively shielded Magnex gradient coil (60 G/cm, 270 μs rise time). The magnet, gradient coil, and IEC gradient power supply were interfaced with an Agilent DirectDrive console (Agilent Technologie, Santa Clara, CA). The acquisition parameters for the spinal cord imaging were: TR ~1200 ms (according to respiratory gating), TE 31 ms, TE 12 ms, 15 ms, 8 5 ms, b-value 1000 s/mm², FOV 1 × 1 cm², data matrix 128 × 128, slice thickness 0.75 mm, NEX 4, NE for MSE 6, diffusion sensitizing gradients 6. The acquisition time was ~72 minutes. The difference in b-value between each echo was less than 1% (~7 s/mm²) of the employed b-value (1000 s/mm²). Data from five controls and five injured animals were reported for the contusion SCI study.

2.4. Comparison of SNR and DTI parameters derived from Magnitude and Phase-Aligned Image Averaging

Region-of-interest (ROI) based comparisons were performed between methods defined on the non-diffusion weighted (B₀) images using ImageJ (NIH, Bethesda, MD). The ROI of the contusion SCI images encompassed the total ventro-lateral WM as indicated in Figure 5. The noise standard deviation of the averaged MSE image, σ , was calculated in consideration of Rician noise distribution by:

$$\sigma = \sqrt{\frac{\sum_{i=1}^L (\text{pixel value})_i^2}{2Ln}}, \quad (4)$$

where *pixel value* is the measured pixel intensity in the noise-only region, L is the total number of pixel, n is the number of echoes (26). The estimated SNR for averaging the phased images was calculated as the ratio of the mean signal intensity to the standard deviation of the noise (26,27,41).

The in vivo DTI parameters, RA, MD, $\lambda_{||}$, and $\lambda_{\perp}$, were compared between SE-Magnitude (NEX=4), SE-Magnitude (NEX=2), MSE-Magnitude (NEX=2, NE=3) and MSE-Phased (NEX=2, NE=3). The SE-Magnitude (NEX=4) is considered as the baseline for comparison. Pearson correlation coefficients (r) with corresponding p-values and Bland–Altman agreement plots were reported for the DTI data derived from SE-Magnitude (NEX=2) and

MSE-Phased (NEX=2) data in comparison to the baseline SE-Magnitude (NEX=4) DTI data. The data were obtained from 5 consecutive slices in 10 animals. A paired student's t-test was performed for statistical tests for DTI parameters in the contusion SCI model to compare the significance and sensitivity level between the control and injured group. The probability of rejecting the null hypothesis was set at p-value < 0.05. Meanwhile, the standardized difference between means (Cohen's d) was also reported to show the effect sizes of each averaging method. A lower effect size, i.e. Cohen's d, indicates a necessity of using larger sample sizes to yield a certain power for a test, and vice versa (42). The DTI data processing and statistics were performed using in house Matlab (MathWorks, Natick, MA) scripts and the statistics toolbox (1,35).

3. Results

The results of signal averaging through complex data, magnitude images and phased images on in vivo mouse spinal cord are shown in figures 2 and 3. The phased images removed the phase difference between successive echoes (Fig. 2) and the phased image averaging maintained a Gaussian noise distribution of a zero mean without noise bias (Fig. 3A–G). Figure 3H and 3I show the theoretical and experimental results of relative SNRs for averaging up to six echoes. Compared to the magnitude image averaging, phased image averaging yielded the highest SNR and provided the best tissue contrast. The contrast-to-noise ratio of the MSE phased image is ~3.87, and that of the magnitude image is ~3.54. MSE phased averaging images in theory have higher SNR than the magnitude averaging images (Fig. 3H). The in vivo experimental data show that the SNR improves when averaging up to three echoes in the GM and WM regions, in contrast to the CSF where more echoes can be averaged due to the longer T_2 relaxation time constant (Fig. 3I). SNRs of the spinal cord B_0 images (NEX=1 for both SE and MSE) were 17.1 ± 1.4 for SE image, 22.2 ± 1.7 for three-echo MSE-Magnitude image, and 31.4 ± 1.8 for three-echo MSE-Phased image.

The image quality of spinal cord DTI RA map was compared between different averaging methods (Fig. 4). The SNRs for the representative SE-Magnitude (NEX=4), SE-Magnitude (NEX=2), MSE-Magnitude (NEX=2, NE=3), and MSE-Phased (NEX=2, NE=3) images are 34.4, 24.2, 31.6, and 44.5, respectively. The MSE-Phased images show the best contrast between GM and WM, even when compared to the SE-Magnitude doubling the scan time. Higher correlations were seen between the derived DTI parameters of MSE-Phased (NEX=2, NE=3) and those of the SE-Magnitude (NEX=4). The difference to the SE-Magnitude (NEX=4) data was generally less for the MSE-Phased data in the Bland-Altman plots (Fig. 4F–I). Figure 5 shows the DTI parameter maps derived from different averaging methods in the contusion SCI study. The MSE-Phased images provided the best image quality with the least noise in all the DTI parameter maps. The measured DTI parameters of the ventro-lateral WM are listed in Table 1. Decreased $\lambda_{||}$ and increased $\lambda_{\perp}$ were evident in the injured WM, suggestive of axonal injury and myelin damage, respectively, at seven days post injury (43). The difference between the control and injured groups was more apparent in the MSE-Phased maps than those in the SE-and MSE-Magnitude maps. The difference was comparable to that obtained by SE-Magnitude with four averages. The MSE-Phased

data showed statistically more significant changes (smallest p-value) with greater effect size (larger Cohen's d) between the control and injured groups.

4. Discussion

Quantitative DTI has been widely used to produce “imaging biomarkers” reflecting the underlying white matter pathology in neurological diseases and injury, such as traumatic brain injury (44), multiple sclerosis (45), optic neuritis (36,46), Alzheimer's disease (47), and SCI (1,3,43). Animal models of neurological disorders have played crucial roles in better understanding mechanisms underlying the functional disabilities and quantitatively validating imaging biomarkers. The employment of rodent models is imperative since histological validation of human subjects is not typically available since biopsy of CNS tissues could impose unnecessary risk to the patient. To image rodent CNS necessitates high resolution to identify the changes associated with small anatomical structures, particularly challenging in mouse spinal cord DTI confronting both the small size (diameter < 2mm) and the susceptibility artifacts from the thoracic cavity and geometric distortions (2,43). High-quality mouse spine DTI was recently reported using conventional SE on an ultra-high field (16.4T) magnet to achieve inplane resolution of $70 \times 70 \mu\text{m}^2$ and 1.0 mm slice thickness with 2-hr acquisition (3); another report using four-shot SE EPI to achieve $100 \times 100 \mu\text{m}^2$ in-plane resolution and 0.75 mm slice thickness on an 11.75T scanner with 42-minute acquisition (8). These studies showcase the advantage of using the ultra-high field MRI to obtain the high-quality mouse spine DTI through the gain in SNR at ultra-high field strength. In the current study we were able to obtain in vivo DTI at $78 \times 78 \mu\text{m}^2$ in-plane resolution and 1 mm slice thickness acquired in 72 min on a 4.7T scanner using the Bayesian phasing approach and diffusion weighted MSE. Our image quality is comparable to those obtained via the ultra-high field scanner, demonstrating the advantage of averaging Bayesian phased multiple spin-echoes.

The effectiveness signal averaging through complex data relies on the consistent phase of the acquired echoes, a condition not attainable in most in vivo measurements dealing with physiological motions including the current MSE and SE datasets (Fig. 2, 3). Therefore, signal averaging of magnitude data has been widely employed in order to avoid the problems involving incoherent phases of the diffusion weighted multiple echoes (21,33,48). Averaging magnitude images increases the measured pixel intensity at the cost of a higher noise level and the introduction of a bias. Phased images improve signal averaging since the zero-mean Gaussian noise distribution is preserved (32). As a result, averaging of the phase-aligned MSE images resolves the phase incoherence complications (Fig. 2) and removes the bias of the elevated Rician noise distribution, achieving the theoretically predicted SNR gain (Fig. 3). This effect is more apparent in the images with low SNR, such as diffusion-weighted images. In the current study, the proposed MSE-Phased approach generated a significantly better SNR gain than the MSE-Magnitude without the elevated Rician noise. It is worth noting that the Bayesian phasing approach could also be applied to gradient echo image, EPI and FSE to appropriately phase images with $\sqrt{2}$ gain in SNR of that in the conventional magnitude images.

Results from *in vivo* experiments indicated that using the MSE-Phased technique could save half of the scan time while still delivering a better DTI quality and consistent diffusion measures. The correlation and Bland-Altman agreement analysis suggested that the MSE variation at half of the acquisition could achieve comparable DTI measurements as the baseline SE measurements (twice acquisition time) (Fig. 4). The shortened acquisition was achieved without degrading image quality allowing precise ROI definition on high-quality images (Fig. 5). The RA maps derived from the MSE-Phased images clearly identified the spared ventro-lateral WM in the contusion epicenter, typically with higher susceptibility artifact confounding EPI-DWI measurements (Fig. 5B). The gain in SNR led to an increased identification of neuropathologies in the mouse SCI using DTI (Table 1).

The optimal number of echoes to be averaged was analyzed in previous and current studies looking for the maximal SNR increase in the targeted tissue (22,33). Short T_2 relaxation time constants limit the number of echoes that could be utilized in signal averaging. In reality, the optimal number of echoes to be added not only depends on the T_2 relaxation of the tissue of interest but also is limited by hardware capabilities, such as field homogeneity, RF refocusing pulse, echo generation and gradient manipulation (24,33,49,50). Sufficient crusher gradient pairs surrounding the refocusing pulses are necessary to reduce stimulated echoes but could also eliminate parts of the magnetization of interest (17,25,51). In our 4.7T spectrometer, the maximum gradient is 62 G/cm with 270 μ s rise time. In a typical data matrix of 128 $\times$ 128 with a 1 cm² field of view, the minimum achievable TE was 12 ms, providing a maximum SNR gain with 3 echoes for signal averaging in the spinal cord WM (Fig. 3I). This MSE diffusion imaging approach was also proved to be successful in acquiring high quality optic nerve imaging with short acquisition time in the *in vivo* study of white matter diffusion fMRI (52) and manganese enhanced MRI (53) using a 4.7T spectrometer.

It is important to note that the Bayesian probability analysis relies on an *a priori* knowledge of the signal amplitude, phase, and noise characteristics. The quality of this prior information influences the accuracy of the resulting phase parameter estimation. Additionally, irregular bulk movement in the diffusion weighted images, which are highly sensitive to motion artifacts, can also introduce significant bias affecting the determination of noise characteristics. Several other methods have been used to deal with issues of averaging in a MSE dataset (29). Although the phase variation between even and odd echoes can be minimized by applying a more sophisticated phase cycling of the RF pulse train, the variation may not be completely eliminated for echo averaging through complex data (24,54,55). To estimate the diffusion coefficient from the averaged magnitude MSE images, approaches such as Rician noise removal (30), or maximum likelihood estimator (29,56) could also be used for better tensor estimation. Finally, a comprehensive joint analysis of all non-averaged echoes, incorporating both estimations of the diffusion measurements as well as the effects of T_2 decay may provide further improvements in the accuracy of the parameter estimates (57,58).

In summary, we have implemented a MSE-Phased acquisition procedure and demonstrated the advantage of improved SNR without an increase in the imaging time, and remedying phase artifacts and correlated noise compared to magnitude averaging. Our results indicate

that averaging the phased MSE images could yield a SNR increase by 80% of the signal in convention SE images. Comparing to the high quality spine DTI in our previous studies (40,59), the current method delivered better image quality by using nearly half of the scan time (72 minutes) required in those studies (~120 minutes). The proposed method should benefit all studies employing diffusion weighted image by substantially improving SNR.

Acknowledgments

This study is supported in part by NIH/NINDS R01 - NS047592, P01- NS 059560 and University of Missouri Spinal Cord Injury Research Program (101506). We gratefully thank Dr. Larry Bretthorst for his valuable advice on the data analysis and manuscript writing, Dr. William Spees for the discussion on the pulse sequence implementation, and Dr. Joshua Chetta for the valuable opinion and discussion on the manuscript preparation.

APPENDIX

Theory of Bayesian phasing analysis

If d_i represents the intensity of the i th pixel in a complex image, then the pixels are related to the phase through a model given by:

$$d_i = A_i \exp\{-i\theta\} + n_i \quad (1 \leq i \leq N), \quad (\text{A-1})$$

where A_i is the amplitude of the i th pixel and θ is the phase, n_i represents the complex noise, with total number of complex data value, N . Separating the complex model into its real parts, d_{Ri} , and imaginary parts, d_{Ii} , one has

$$d_{Ri} = A_i \cos\theta + n_{Ri}, \quad (\text{A-2})$$

$$d_{Ii} = -A_i \sin\theta + n_{Ii}, \quad (\text{A-3})$$

where n_{Ri} and n_{Ii} represent the real and imaginary parts of the complex noise. Given the prior probability of noise standard deviation, σ , the data, D , and the background information I , the posterior probability for the phase, $P(\theta|\sigma DI)$, is computed by applying Bayes' theorem:

$$P(\theta|\sigma DI) = \frac{P(\theta|\sigma I)P(D|\sigma\theta I)}{P(D|\sigma I)}, \quad (\text{A-4})$$

where the prior probability for the phase, $P(\theta|\sigma I)$, represents what is known about the phase before acquiring the data. The direct probability for the data, $P(D|\sigma\theta I)$, is a marginal probability from which the dependence on the amplitudes has been removed, and $P(D|\sigma I)$ is a normalization constant. If this probability density function is normalized at the end of the calculation, one obtains

$$P(\theta|\sigma DI) \propto P(\theta|I)P(D|\sigma\theta I). \quad (\text{A-5})$$

Applying the sum and product rules of the probability theory and omitting constant terms that will cancel upon normalization, the posterior probability can be rewritten as:

$$P(\theta|\sigma DI) \propto P(\theta|I) \int dA P(A|\sigma I) P(D|A\theta\sigma I), \quad (\text{A-6})$$

where $P(A|\sigma I)$ is the joint prior probability for the amplitudes. The probability for the data, i.e. the likelihood, given the parameters is represented by $P(D|A\theta\sigma I)$. The prior probability for θ will be assigned a uniform bounded prior:

$$P(\theta|I) = \begin{cases} \frac{1}{2\pi} & \text{if } 0 \leq \theta \leq 2\pi \\ 0 & \text{otherwise} \end{cases}. \quad (\text{A-7})$$

The amplitude prior will be assigned as a generalized Gaussian of the form:

$$P(A|\beta\sigma I) \propto \sigma^{-N} \exp\left\{-\frac{\beta^2}{2\sigma^2} \sum_{k=1}^N \sum_{l=1}^N A_k U_{kl} A_l\right\}, \quad (\text{A-8})$$

where the hyperparameter, β , part of I , expresses how strongly this prior information is believed, and the matrix, U_{kl} specifies how the amplitudes are related to each other. The derivations of the estimated amplitudes and the posterior probabilities are given in Bretthorst, here we just give the results: the image voxels are given by:

$$\sum_{l=1}^N V_{kl} \hat{A}_l = d_{Rk} \cos\theta + d_{Ik} \sin\theta, \quad (\text{A-9})$$

where

$$V_{kl} = \delta_{kl} + \beta^2 U_{kl}, \quad (\text{A-10})$$

where δ_{kl} is a Kronecker delta function. Equation (A-9) can be rewritten as:

$$\hat{A}_l \equiv \hat{a}_l \cos\theta + \hat{b}_l \sin\theta, \quad (\text{A-11})$$

where $\hat{a}_i$ and $\hat{b}_i$ are the coefficients in equation (A-9) multiplying through by the inverse of the matrix. The V_{kl} posterior probability for the phase then has the form of:

$$P(\theta|\sigma DI) \propto \exp\left\{\frac{\sqrt{W^2 + X^2} \cos(2\theta + \varphi)}{4\sigma^2}\right\}, \quad (\text{A-12})$$

where W, X are given by,

$$W \equiv \sum_{i=1}^N (\hat{a}_i d_{Ri} - \hat{b}_i d_{Ii}), \quad (\text{A-13})$$

$$X \equiv -\sum_{i=1}^N (\hat{a}_i d_{Ii} + \hat{b}_i d_{Ri}), \quad (\text{A-14})$$

and

$$\varphi = \tan^{-1} \frac{X}{W}. \quad (\text{A-15})$$

Taylor expanding Eq. (A-15) around $\theta_{max} = -0.5\theta$, the estimated phase is given by:

$$\hat{\theta} = \theta_{max} \pm \sqrt{\frac{8\sigma^2}{\sqrt{W^2 + X^2}}}. \quad (\text{A-16})$$

Finally, the phased images can be generated according to the following equation:

$$S_{pi} = S_i \exp\{-i\hat{\theta}\}, \quad (\text{A-17})$$

where the S_{pi} is the phased signal, S_i is the original signal, and $\hat{\theta}$ is the estimated voxel-wise phase. The phased signals can be projected entirely to the real channel.

The Bayesian phasing analysis is accessible free of charge from the program of “The Bayesian Analysis of Common NMR problems software” for noncommercial use. The software is available through the World Wide Web link at: <http://bayesiananalysis.wustl.edu/>.

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Figure 1.

Diffusion weighted MSE pulse sequence diagram. A conventional pulsed gradient SE diffusion preparation is followed by a multiple-echo readout. The phase encode step and the diffusion gradient pair are outside the MSE acquisition loop ensuring each of the multi-slice MSE undergoing the same diffusion weighting in the same k-space line. A crusher gradient pair is added with the refocusing pulse to eliminate secondary echoes by alternating the sign for each successive echo.

Figure 2.

Bayesian phasing analysis removes phase differences between successive echoes. In vivo mouse spinal cord images of the first (upper panel, A–D) and second (lower panels, E–H) echoes are displayed. The k-space center (marked in red) is shifted along the geometric center of the image (marked in green) between the first and second echo (B, F), as a result of phase variation seen in the MSE phase images (C, G). After appropriately phasing to generate the phase-aligned images, no such phase variation between echoes is seen in the phased images (D, H). The spinal cord is marked in yellow.

Figure 3.

Averaging phased images removes phase artifacts and preserves the noise characteristics in complex data. Averaging MSE images by complex values results in an artifact (arrows) due to incoherent phases between successive echoes (A). Averaging magnitude images removes the phase artifact but results in non-zero offset Rician noise distribution which reduces the SNR improvement and may bias the diffusion tensor parameter estimates (B). Averaging phased images eliminates errors due to phase artifacts and Rician noise (C). These phased images display the greatest SNR among the three reconstruction methods and provide better tissue contrast in the spinal cord. The images shown here are on the same intensity scale. The noise level of each image is shown in the expanded rectangular region (D–F). Note that the non-zero mean Rician noise elevates the mean pixel intensity in the magnitude-averaged image (E). The noise distributions are measured in the noise-only region (G). The measured pixel intensity of the MSE image, M , is normalized by its noise standard deviation, σ . The relative SNR gains of the averaged MSE images up to six echoes were estimated from theoretical (H) and experimental (I) dataset. Theoretically, in the WM region, the SNR of the phased image improves to 2.46-fold of the single echo acquisition when averaging up to

6 echoes while that of the magnitude image averaging increases to only 1.74-fold of the single echo acquisition. In reality, the experimental data shows that the SNR tapers off after 3 echoes for both GM and WM. Compared to the single SE image, the SNRs gain plateaus at 1.84-fold for the phased image and 1.30-fold for magnitude image in the WM region.

Figure 4.

In vivo spinal cord anatomical B_0 image (A) and the RA maps of mouse spinal cord derived from SE data with four magnitude averaging (B), SE data with two magnitude averaging (C), three echo MSE data with two magnitude averaging (D), and three echo MSE data with two phased averaging (E). SNRs for the representative SE-Magnitude (NEX=4), SE-Magnitude (NEX=2), MSE-Magnitude (NEX=2, NE=3), and MSE-Phased (NEX=2, NE=3) images are 34.4, 24.2, 31.6, and 44.5, respectively. The values of RA (F), MD (G), $\lambda_{||}$ (H), and $\lambda_{\perp}$ (I) derived from SE-Magnitude (NEX=2) and MSE-Phased (NEX=2, NE=3) were analyzed for correlation (left panel) and agreement (right panel) with the values of gold standard SE-Magnitude (NEX=4) data. Blue: MSE-Phased (NEX=2) vs SE-Magnitude (NEX=4); Red: SE-Magnitude (NEX=2) vs SE-Magnitude (NEX=4). The solid and dash lines in the Bland-Altman agreement plots indicate mean ± 1.96 standard deviation for each comparison (in respective colors). MSE-Phased data shows higher correlation and degree of agreement in compared with gold standard SE-Magnitude data with four averaging.

Figure 5.

Diffusion parameter maps of spinal cords from the control (A) and contusion SCI (B) mice. The ventro-lateral WM areas are marked using a red line. The MSE-Phased maps clearly show superior image quality in the mouse spinal cord to the SE- or MSE-Magnitude images. Severe spinal cord atrophy at 7 days after contusion is apparent. A dorsal to ventral decrease in injury severity is evidenced by the hypo-intense inner region of ventro-lateral WM in both RA and $\lambda_{||}$ maps, as well as the hyper-intense inner region of the $\lambda_{\perp}$ map.

Table 1
Comparison of SE-Magnitude, MSE-Magnitude and MSE-Phased derived diffusion tensor parameters.

Method	Group	RA	$\lambda_{\parallel}(\mu\text{m}^2/\text{ms})$	$\lambda_{\perp}(\mu\text{m}^2/\text{ms})$	MD($\mu\text{m}^2/\text{ms})$
SE-Magnitude (NEX=4)	Control	1.02±0.03	1.94±0.12	0.25±0.02	0.82±0.03
	Injury	0.60±0.04	1.30±0.04	0.42±0.03	0.76±0.03
SE-Magnitude (NEX=2)	Control	0.93±0.04	1.80±0.14	0.31±0.03	0.89±0.05
	Injury	0.62±0.08	1.38±0.10	0.46±0.07	0.83±0.06
SE-Magnitude (NEX=2, NE=3)	Control	0.98±0.02	1.82±0.13	0.29±0.03	0.82±0.06
	Injury	0.60±0.05	1.32±0.09	0.45±0.04	0.74±0.01
MSE-Absorption (NEX=2, NE=3)	Control	1.03±0.03	1.96±0.13	0.28±0.02	0.81±0.06
	Injury	0.59±0.04	1.29±0.06	0.43±0.02	0.76±0.02