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SNR-Enhancing Joint Reconstruction for Improved Diffusion Imaging of Mouse Spinal Cord White Matter Injury

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Abstract

Purpose—To assess the capability of signal-to-noise ratio enhancing reconstruction (SER) to reduce the acquisition time for quantitative white matter injury assessment.

Methods—Four single-average diffusion tensor imaging (DTI) datasets were acquired for each animal from 4 mouse cohorts: two models of spinal cord injury and two control groups. Quantitative parameters (apparent diffusion coefficient, relative anisotropy, axial and radial diffusivities) were computed from (I) single-average data with traditional reconstruction; (II) single-average data with SER; (III) 4-average data with traditional reconstruction; and (IV) single-average data with optimized multicomponent nonlocal means (OMNLM) denoising. These approaches were compared based on coefficients of variation (COVs) and whether estimated diffusion parameters were sensitive to injury.

Results—SER yielded better COVs for diffusivity and anisotropy than traditional reconstruction of single-average data, and yielded comparable COVs to that achieved with 4-average data. In addition, diffusion parameters obtained using SER with single-average data had comparable injury sensitivity to those obtained from 4-average data, while diffusion parameters obtained from OMNLM and traditional reconstruction of single-average data had limited sensitivity.

Conclusion—A 4-fold reduction in the number of averages for quantitative diffusion imaging of small animal white matter injury is feasible using SER. Our results also underscore the need to validate nonlinear methods using task-based measures on an application-by-application basis.

Keywords

diffusion tensor imaging; signal-to-noise ratio; denoising

Introduction

Diffusion-weighted MR (DW-MR) imaging can be used to examine the microstructural characteristics of biological tissues, and recent work has shown that DW-MR imaging

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enables quantitative assessment of injury in various central nervous system pathologies in both clinical and preclinical studies (1–4). MR imaging studies of rodent models provide golden opportunities to compare parameters derived from DW-MR imaging with tissue morphology or pathophysiology from postmortem histology, and the results from such studies are critical for understanding the white matter pathophysiology of specific neurological functions (5). However, the small size of the rodent central nervous system necessitates high image resolution and correspondingly lower signal-to-noise ratio (SNR) to avoid partial volume effects. Low SNR substantially reduces the accuracy of quantitative parameters derived from DW-MR imaging (6,7).

In preclinical studies, substantial signal averaging is often used to improve SNR. However, acquiring multiple averages increases imaging time, which can be stressful for imaging subjects and limits throughput. Thus, the ability to enhance SNR without lengthening scan time or sacrificing spatial resolution would substantially improve preclinical DW-MR experiments.

A large number of different DW-MR denoising methods have previously been investigated to enhance SNR, many of which are reviewed in (8). However, to the best of our knowledge, no previous denoising methods have been validated in the context of injured tissue. It is important to note that the diffusion signal from injured tissue differs, sometimes in subtle ways, with that from healthy tissue. For example, in a typical DW-MR experiment involving the healthy human brain, tissue diffusion characteristics often vary smoothly over relatively large spatial regions. On the other hand, tissue injury can lead to highly-localized changes in the diffusion parameters, sometimes comprising just a handful of voxels. This means that the assumptions typically used to accurately denoise DW-MR signal in healthy tissue are not necessarily applicable to injured tissues, and that existing DW-MR denoising methods must be validated with injured tissues before their use, with confidence, in prospective imaging studies.

Recently, Haldar *et al.* reported a statistical reconstruction method for increasing the SNR of DW-MR images (8). This method performs joint penalized maximum-likelihood reconstruction of the DW-MR images from complex-valued k -space data, using a specially-designed regularization penalty that leverages the fact that different DW-MR images from the same subject are typically smooth with edge features, and generally have correlated image edge features (despite having potentially very different image contrast). Compared to alternative approaches, the SNR-enhancing reconstruction (SER) method from (8) is flexible enough to accommodate arbitrary q -space sampling schemes, and enables high-quality edge-preserving denoising while simultaneously providing theoretical characterizations of the resolution and SNR of the reconstructed images. In addition, these theoretical resolution and SNR characteristics enable the data acquisition and image reconstruction process to be optimized for SNR efficiency, achieving an optimal balance between resolution and SNR for a fixed amount of data acquisition time (8–10). While SER was evaluated for a range of different application settings in (8) (including simulated healthy mouse brain diffusion tensor imaging (DTI), healthy human brain DTI for several different b -values, and healthy human brain diffusion spectrum imaging) and was shown to yield excellent performance, the approach was not evaluated in the context of injured tissue.

In this work, we studied whether or not SER can be used to accelerate data acquisition for DW-MR experiments that assess white matter injury in mouse models of traumatic spinal cord injury and multiple sclerosis. Our mouse spinal cord DW-MR experiments have similar characteristics to other small animal imaging experiments, and denoising for these injury models is arguably more challenging than the imaging scenarios considered in (8). A preliminary account of portions of this work was originally presented in (11).

Methods and Materials

Animal Preparation

Twenty ten-week-old female C57BL/6 mice weighing 18 ~ 20 g (Harlan, Indianapolis, IN) were used. Two animal models were generated, including contusion spinal cord injury at T10 spinal cord (5 sham control and 5 injury) and EAE (experimental autoimmune encephalomyelitis, a mouse model of multiple sclerosis, 5 control and 5 EAE) as in previous reports (12,13). All animal handling, including surgical intervention and pre- and post-surgical care, was performed 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 Institutional Care and Use Committee.

Data Collection

Data was acquired at 4.7T (Agilent Inc., Palo Alto, CA) following previous reports (12,14). Briefly, a conventional spin-echo imaging sequence with Stejskal-Tanner diffusion weighting gradients was used (15). *In vivo* DTI data was acquired with TE/TR 38/1200 ms, FOV 1.0 cm $\times$ 1.0 cm, slice thickness 0.75 cm, $\delta = 21/7$ ms producing $b = 1.0$ ms/ μm^2 , 6 diffusion directions, respiratory gating, and a 128×128 acquisition matrix resulting in $78 \mu\text{m} \times 78 \mu\text{m}$ in-plane resolution (16). Four consecutive repetitions of a single-average DW-MR protocol were acquired from each animal and stored separately. DW-MR images were obtained covering T10 spinal cord for the contusion injury/sham control mice, and covering L2 spinal cord for EAE/control mice.

Data Processing

DW-MR images were jointly reconstructed from a single average of the measured k -space data, using the SER method from (8). This reconstruction enforces image smoothness to enhance SNR, while explicitly modeling and preserving the edge information that is shared between the different DW-MR images. Regularization parameters were adjusted automatically to achieve a 4-fold reduction in noise variance for the spinal cord parenchyma, as described in (8). These parameter settings yield a less than 10% loss of spatial resolution along each direction, and a time-efficient balance between resolution and SNR (8,9) relative to conventional Fourier reconstruction. Subsequently, DTI parameters were estimated from (I) conventional Fourier reconstructions of single-average data, (II) SER reconstructions of single-average data, and (III) conventional Fourier reconstructions of 4-average data. Note that conventional Fourier reconstruction is the standard technique for many small animal DW-MR studies (12–14,16).

For comparison, we also estimated DTI parameters after applying optimized multicomponent nonlocal means (OMNLM) denoising (17) to the complex images generated from traditional reconstruction of single-average data. OMNLM is based on the assumption that the diffusion signal in any given voxel will be similar to the diffusion signal from other (potentially distant) spatial locations within the image, and that SNR can be enhanced by averaging voxels with similar signal characteristics. SER was compared against OMNLM in (8), and the approaches were demonstrated to yield similar performance in terms of diffusion indices when applied to data representing healthy tissue (though SER also had theoretical characterization that was not available for OMNLM). Our implementation of OMNLM is the same as described in (8), and uses the parameter settings from (17) which depend on an estimate of the noise variance. To improve scan efficiency, our acquisitions use tight FOVs with substantial aliasing, with the aliasing designed in a way that does not create artifacts in the spinal cord parenchyma. However, these tight FOVs also mean that few “noise-only” voxels are available to be used for conventional noise variance estimation. As a result, we have used a popular wavelet-based robust noise variance estimation method described in section 4.2 of (18).

Data Analysis

Diffusion tensors were estimated from the DW-MR images using a weighted linear least-squares method (19), and eigenvalues and DTI parameters (including relative anisotropy (RA), apparent diffusion coefficient (ADC), and both axial and radial diffusivity) were calculated with an in-house Matlab program (20).¹ As described previously (12–14,16,20), the parenchyma of spinal cord was manually identified using ADC maps, and regions of interest (ROIs) were drawn manually based on tissue contrast from RA maps. Quantitative analysis was conducted using ImageJ 1.46 (<http://imagej.nih.gov/ij/>). Student’s t-tests were performed using Origin 9.1 (<http://www.originlab.com>) to compare quantitative DTI parameters. Statistical significance was accepted as $p < 0.05$.

Results

Representative *in vivo* DTI-derived parameter maps from a naïve C57BL/6 female mouse spinal cord are shown in Fig.1. For all DTI parameter maps the single-average data with SER (Fig. 1b, f, and j) showed comparable image quality to that of 4-average data with traditional reconstruction (Fig. 1c, g, and k), while the single-average data with traditional reconstruction (Fig. 1a, e, and i) suffered from noise contamination. The most significant noise effect is most clearly observed in the RA of the ventrolateral gray matter (VLGM). The mean VLGM RA for single-average data with traditional reconstruction (0.35 ± 0.05) was significantly larger ($p < 0.001$) than that for SER images from single-average data (0.27 ± 0.03) and traditional reconstruction of 4-average data (0.26 ± 0.03). SER was successful in mitigating noise bias in single-average data, with no statistically-significant differences between single-average SER and 4-average traditional reconstruction (Fig. 1m and n). OMNLM is observed to have much lower spatial variation in the diffusion parameter

¹The Matlab code used for fitting tensors and estimating tensor parameters has recently been incorporated into the freely-available BrainSuite Diffusion Pipeline software (<http://brainsuite.org/processing/diffusion/>).

estimates within each ROI compared to the other approaches. However, the estimated diffusion parameter values for OMNLM are significantly different (lower axial diffusivity, higher radial diffusivity, and lower RA) from the parameter values estimated with either single-average SER or traditional reconstruction of 4-average data, indicating a substantial bias.

A quantitative comparison between the different approaches was performed based on the coefficient of variation (COV), the ratio between the standard deviation and the mean, which will be small when the diffusion indices have high “SNR.” COVs were computed in four different ROIs: dorsal white matter (DWM), ventrolateral white matter (VLWM), dorsal gray matter (DGM), and VLGM. Results are shown in Table 1. For all observed DTI parameters, no statistically significant difference was observed between the single-average data with SER and the 4-average data with traditional reconstruction. However, the single-average data with traditional reconstruction had larger COVs, sometimes almost twice as large with substantial statistical significance, $p < 0.001$. As might be expected from the smooth appearance of the images in Fig. 1, OMNLM yielded the smallest COVs. COVs are sensitive to OMNLM’s small variance, but not to its substantial bias.

Following a previous report (13), we also quantified the amount of “spared VLWM” for mice with traumatic spinal cord injury. The procedure for identifying spared VLWM is shown in Fig. 2a – c. The spared VLWM was determined by using thresholds based on the mean ± 2 standard deviations computed from the VLWM RAs of control mice (based on 4-average data with traditional reconstruction). Results are shown graphically in Fig. 2h – n and numerically in Table 2. Both traditional reconstruction and OMNLM denoising of single-average data yielded a significantly different ($p < 0.01$) extent of spared VLWM relative to traditional reconstruction of 4-average data. Specifically, the results from traditional reconstruction of single-average data substantially overestimated the spared VLWM (many false positives), while the results from OMNLM denoising substantially underestimated the spared VLWM (many false negatives). On the other hand, SER of single-average data yielded a comparable estimate of spared VLWM to traditional reconstruction of 4-average data.

Results from the L2 spinal cord of EAE and control mice are shown in Fig. 3. For both the control and EAE groups, the single-average data with traditional reconstruction suffers from low SNR. However, similar to the previous case, SER substantially improved image quality for both EAE and control mice. The yellow arrows in Figs. 3e–h point to a white matter lesion with abnormal diffusivity, which is easily visualized in most of the EAE reconstructions (except, perhaps, for OMNLM). However, both traditional reconstruction and OMNLM denoising of single-average data failed to show a statistically significant difference between the control and EAE groups, while both single-average data with SER and 4-average data with traditional reconstruction yielded similar statistically significant differences between the two groups (Fig. 3i).

Discussion

The application of SER to single-average data from both naïve and injured mouse spinal cords effectively reduced noise, and produced diffusion parameter estimates that closely matched those obtained from conventional 4-average data, enabling sensitive identification of microstructural white matter changes. In contrast, the diffusion parameters derived from single-average data with traditional reconstruction were heavily biased because of low SNR, with potentially lower sensitivity to microstructural tissue changes. Importantly, the substantial gain in SNR obtained with SER is associated with only a minor loss of spatial resolution (8–10). Due to its theoretical characteristics (8), SER is expected to have similar advantages if applied to the joint reconstruction of other types of MR images with similar characteristics to those considered in this work (10,21).

Our results also highlight the need to test nonlinear methods in task-based application-specific contexts, instead of relying solely on more general validation studies that emphasize generic image quality metrics. Specifically, while SER and OMNLM denoising performed similarly for the datasets and image quality metrics used in Ref. (8), the two methods performed quite differently from each other in the present application-specific task-based validation study, with SER demonstrating substantial advantages. The need for task-based validation is not a new idea (22–24), though application-specific validation studies of nonlinear methods are less common than perhaps they should be.

We would like to emphasize our results do not suggest that SER should always be preferred over OMNLM (or any other denoising method) in arbitrary DW-MR applications. Both SER and OMNLM are nonlinear methods that make specific assumptions about the DW-MR image sequence, and these assumptions may be more or less accurate in different application scenarios.

Compared to previous evaluations of OMNLM, we believe that its relatively poor performance in this specific application is related to the important, though potentially subtle, high-resolution image features that are present in small animal injury DW-MR images, but which are either not present or less important in DW-MR experiments of healthy tissue. Specifically, OMNLM is enabled by the assumption that there are a sufficiently large number of image patches with similar diffusion characteristics and similar spatial features, but this assumption is not satisfied for relatively rare image features that change substantially over short length scales relative to the image resolution. This forces OMNLM to average together voxels that are not necessarily very similar to each other, leading to a loss of important image features. We believe that modifications to OMNLM could be made to avoid reduce the impact of this issue, though such extensions are beyond the scope of this work.

Conversely, we also expect there to be scenarios in which SER might not perform as well as it did in this study. Specifically, SER is based on the assumption that localized edge-preserving spatial smoothing will enhance image SNR without degrading the ability to extract important information from the dataset. This assumption will not hold true if the image features of interest are too small. For example, if the feature of interest is the size of a

single voxel, then edge-preserving spatial smoothing would either fail to denoise the voxel (because an edge was detected, and no spatial smoothing is performed across the edge), or would exacerbate partial volume artifacts (because the edge was not detected, and the feature of interest was accidentally averaged with neighboring voxels that have distinct diffusion characteristics). These kinds of assumption violations can be largely avoided by applying SER to datasets where the features of interest are large in comparison to the voxel size. Theoretically, this is also the regime where SER is expected to yield the highest SNR/resolution efficiency (8–10). See Ref. (8) for further discussion.

Conclusions

In this work, we demonstrated that the SER denoising strategy from Ref. (8) can be used in place of averaging, leading to experiments that are 4 times faster but which are still capable of detecting white matter injury in mouse models of multiple sclerosis and traumatic injury. As far as we are aware, this is the first time that any DW-MR denoising methods have been evaluated in the context of white matter injury assessment. We expect our results to provide useful insight for the design of future DW-MR experiments involving similar small animal injury models. However, due to the nonlinearity of SER and most other state-of-the-art denoising methods, additional validation should be performed for application contexts and denoising methods that are very different from those considered here or in previous literature.

It should be noted that a software implementation for a variation of the SER reconstruction method used in this work is available for download from <http://mr.usc.edu/download/joint-denoising-for-diffusion-mri-magnitude-images>. However, different from the algorithm used in Ref. (8) and this work, this software implementation handles magnitude images with Rician or non-central chi statistics (25) instead of complex k -space data with Gaussian noise.

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Figure 1.

Representative *in vivo* diffusion tensor imaging (DTI) parameter maps from a naïve C57BL6 female mouse at T10 spinal cord. Relative anisotropy (RA, a – d), radial diffusivity ($\lambda_{\perp}$, e – h), and axial diffusivity ($\lambda_{\parallel}$, i – l) maps are shown for single-average data with traditional reconstruction (a, e, and i), single-average data with SER (b, f, and j), 4-average data with traditional reconstruction (c, g, and k), and single-average data with OMNLM denoising (d, h, and l). The solid red lines delineate region of interest (ROI) boundaries. The ROIs labels are indicated in panel (i): dorsal white matter (DWM), ventrolateral white matter (VLWM), dorsal gray matter (DGM), and ventrolateral gray matter (VLGM). The quantified RA, $\lambda_{\parallel}$, and $\lambda_{\perp}$ values for single-average data with traditional reconstruction (vertical lines), single-average data with SER (gray), 4-average data with traditional reconstruction (white), and single-average data with OMNLM denoising (black) are shown in panels (m) and (n). Statistically significant differences are shown with * and # symbols, which represent $p < 0.05$ and 0.001 respectively.

Figure 2.

Quantification of “spared ventrolateral white matter” (VLWM) for female C57BL6 mice with contusion injuries at the T10 spinal cord. A binary mask defining the region of spared VLWM was determined by thresholding RA, as shown in panels a – c. The mean and standard deviation of RA for naïve C57BL6 mice VLWM were obtained from 4-average data with traditional reconstruction (a, also see Fig. 1c). For the injured mice, VLWM voxels were defined as “spared” if the RA was within the range defined by the control mice mean $\pm$ 2 standard deviations. Applying this approach to (b) RA maps from injured mice

leads to a (c) precise segmentation of spared VLWM. The solid red line in (c) delineates the boundary of the spared VLWM ROI. Representative RA maps (d – g) and spared VLWM (h – k) determined by RA thresholding are shown for single-average data with traditional reconstruction (d and h), single-average data with SER (e and i), 4-average data with traditional reconstruction (f and j), and OMNLM denoising of single-average data (g and k). Panels (l – n) respectively show the overlap (yellow) between the spared VLWM estimated from 4-average data (green) from panel (j) with the spared VLWM estimated using the other methods (red) from panels (h), (i), and (k). Voxels where the spared VLWM ROIs overlapped are shown in yellow See Table 2 for quantitative results.

Figure 3.

Representative maps of *in vivo* DTI-derived axial diffusivity ($\lambda_{||}$) at the L2 spinal cord of female C57BL6 mice and quantified ventrolateral white matter (VLWM) $\lambda_{||}$. The axial diffusivities ($\lambda_{||}$) of one control mouse (a – d) and one EAE mouse (e – h) are shown for single-average data with traditional reconstruction (a and e), single-average data with SER (b and f), 4-average data with traditional reconstruction (c and g), and OMNLM (d and h). The solid line delineates the region of interest for the VLWM. Quantitative results for the VLWM ROI are shown in panel (i) where I, II, III, and IV correspond to single-average data with traditional reconstruction, single-average data with SER, 4-average data with traditional reconstruction, and single-average data with OMNLM denoising, respectively. The data is presented as mean $\pm$ standard deviation ($n = 5$ mice), for control (white) and EAE (black) mice. *: $P < 0.01$.

Table 1
Coefficients of variation for naïve C57BL6 female mouse spinal cord DTI parameters at T10 spinal cord (n = 5)

	I	II	III	IV
Relative Anisotropy (RA)	DWM	0.22 ± 0.04	0.16 ± 0.05	0.11 ± 0.03 ^{##}
	VLWM	0.25 ± 0.03	0.21 ± 0.03 ^{\$}	0.18 ± 0.02 [*]
	DGM	0.36 ± 0.04	0.29 ± 0.04	0.29 ± 0.07
	VLGM	0.43 ± 0.04	0.40 ± 0.07	0.34 ± 0.06 [*]
Axial Diffusivity ($\lambda_{ }$, $\mu\text{m}^2/\text{ms}$)	DWM	0.29 ± 0.08	0.21 ± 0.13	0.20 ± 0.07
	VLWM	0.25 ± 0.04	0.18 ± 0.03 ^{\$}	0.16 ± 0.02 ^{**}
	DGM	0.28 ± 0.05	0.18 ± 0.05 ^{\$}	0.15 ± 0.03 ^{**}
Radial Diffusivity ($\lambda_{\perp}$, $\mu\text{m}^2/\text{ms}$)	DWM	0.61 ± 0.19	0.47 ± 0.24	0.43 ± 0.17
	VLWM	0.66 ± 0.12	0.51 ± 0.11 ^{\$}	0.47 ± 0.08 [*]
	DGM	0.39 ± 0.11	0.23 ± 0.08 ^{\$}	0.21 ± 0.04 [*]
ADC ($\mu\text{m}^2/\text{ms}$)	VLGM	0.26 ± 0.03	0.14 ± 0.02 ^{\$\$}	0.13 ± 0.02 ^{**}

I: single-average data with traditional reconstruction.

II: single-average data with SNR-enhancing reconstruction.

III: 4-average data with traditional reconstruction.

IV: single-average data with OMNLM denoising.

DWM: dorsal white matter, VLWM: ventrolateral white matter, DGM: dorsal gray matter, VLGM: ventrolateral gray matter.

^{\$}: $p < 0.05$ between I and II.

^{*}: $p < 0.05$ between I and III.

[#]: $p < 0.05$ between I and IV.

^{\$\$}: $p < 0.001$ between I and II.

^{**}: $p < 0.001$ between I and III.

^{##}: $p < 0.001$ between I and IV.

Spared ventrolateral white matter (VLWM) fractions for C57BL6 female mice with a contusion injury at T10 spinal cord.

Table 2

Spared VLWM (%)					p-value vs III			
	I	II	III	IV	I	II	IV	
Spared VLWM (%)	43.1 ± 5.8	26.0 ± 4.1	24.7 ± 3.7	13.7 ± 4.5	0.00033	0.61	0.0071	
Overlap (%)	58.2 ± 7.6	65.2 ± 6.6		32.1 ± 5.3				

I: single-average data with traditional reconstruction.
II: single-average data with SNR-enhancing reconstruction.
III: 4-average data with traditional reconstruction.
IV: single-average data with OMNLM denoising.

The spared VLWM was normalized by the total VLWM area of naïve T10 mouse spinal cord. (see Fig. 1).