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Optimization of Selective Inversion Recovery Magnetization Transfer Imaging for Macromolecular Content Mapping in the Human Brain

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Abstract

Purpose—To optimize a selective inversion recovery (SIR) sequence for macromolecular content mapping in the human brain at 3.0 T.

Methods—SIR is a quantitative method for measuring magnetization transfer (qMT) that employs a low-power, on-resonance inversion pulse. This results in a biexponential recovery of free water signal that can be sampled at various inversion/predelay times (t_i/t_D) to estimate a subset of qMT parameters, including the macromolecular-to-free pool-size-ratio (*PSR*), the R_1 of free water (R_{1f}), and the rate of MT exchange (k_{mf}). The adoption of SIR has been limited by long acquisition times (≈ 4 mins/slice). Here, we use Cramér-Rao Lower Bound theory and data reduction strategies to select optimal t_i/t_D combinations to reduce imaging times. The schemes were experimentally validated in phantoms, and tested in healthy volunteers ($N=4$) and a multiple sclerosis patient.

Results—Two optimal sampling schemes were determined: *i*) a 5-point scheme (k_{mf} estimated) and *ii*) a 4-point scheme (k_{mf} assumed). In phantoms, the 5/4-point schemes yielded parameter estimates with similar signal-to-noise ratios as our previous 16-point scheme, but with 4.1/6.1-fold shorter scan times. Pair-wise comparisons between schemes did not detect significant differences for any scheme/parameter. In humans, parameter values were consistent with published values, and similar levels of precision were obtained from all schemes. Furthermore, fixing k_{mf} reduced

the sensitivity of *PSR* to partial-volume averaging, yielding more consistent estimates throughout the brain.

Conclusions—qMT parameters can be robustly estimated in 1 min/slice (without independent measures of B_0 , B_1^+ , and T_1) when optimized t_1 – t_D combinations are selected.

Keywords

quantitative magnetization transfer; optimization; selective inversion recovery; myelin; cross-relaxation

INTRODUCTION

In addition to mobile water protons, from which conventional MRI signals are derived, biological tissue contains an abundance of protons associated with immobile macromolecules. Because these macromolecular protons exhibit very short transverse relaxation times ($\approx 10 \mu\text{s}$), they do not directly contribute to the observed signals in conventional imaging sequences. These macromolecular protons do, however, indirectly affect the observed water proton signal via magnetization transfer (MT) processes, including chemical exchange and/or dipolar interactions. In neural tissue, protons associated with myelin lipids are a large source of MT contrast (1,2). As a result, MT contrast has been used to assay changes in myelination related to disease (3–6), as well as during normal development (7) and aging (8).

Any radiofrequency (RF) pulse that perturbs the thermal equilibrium between macromolecular and water protons (i.e., affects the pools differently) generates MT contrast. Most commonly, an off-resonance RF pulse is applied to selectively saturate the broad macromolecular pool (9), and the resulting decrease in the water proton signal is characterized by the magnetization transfer ratio (MTR). Although MTR correlates with myelin content (10,11), it is also sensitive to experimental parameters (12) (e.g., MT offset frequency, B_1^+ variations, TR) and tissue relaxation times (13). In contrast, quantitative MT (qMT) approaches (13,14) are able to quantify distinct tissue parameters from a two-pool model of the MT effect, rather than the combined effect of acquisition and tissue parameters. For example, qMT-derived measures of the macromolecular-to-free proton pool size ratio (*PSR*) have been shown to relate more closely with myelin content than MTR (10,15–17).

Pulsed saturation qMT imaging, where off-resonance MT pulses are interleaved with a steady-state imaging acquisition (18,19), can be readily employed on clinical systems. Using this approach, qMT data are collected at various MT pulse offset frequencies and amplitudes. The resulting data are then fit with a two-pool model to determine $PSR = M_{0m}/M_{0f}$, the rate of MT exchange from macromolecular to free pools ($k_{mf} = k_{fm}/PSR$ assuming mass balance), and the relaxation rates of each pool (R_{1f} , R_{1m} , R_{2f} , and R_{2m}) — here the subscripts *m* and *f* denote *free* and *macromolecular* pools, respectively. Unfortunately, pulsed saturation qMT often requires long scan times for whole-brain imaging. To reduce scan times, the number of pulsed saturation images required to invert the model can be reduced by designing optimal sampling strategies (20,21) or by fixing certain parameters during the fitting procedure (22). Even with these strategies, independent

estimates of B_0 , B_1^+ , and T_1 are required to invert the two-pool model, resulting in data acquisition and analysis schemes that are complicated and difficult to implement in certain scenarios (e.g., when motion is present).

Selective inversion recovery (SIR) imaging (23–25) is an alternate approach that does not require independent estimates of B_0 , B_1^+ , and T_1 . SIR is based upon the application of a low-power, on-resonance inversion pulse, which inverts water protons with minimal impact on macromolecular protons. The resulting biexponential recovery of the free water signal is then sampled at various inversion times (t_i) to estimate a subset of qMT parameters (PSR , k_{mf} , R_{1f} , and M_{0f}) along with a parameter (S_f) that accounts for non-ideal inversion of the free water signal. We have previously developed a SIR sequence with a fast spin-echo (SIR-FSE) acquisition for applications in human brain at 3.0 T (26). Although our preliminary findings were promising, the proposed SIR-FSE protocol was too slow for most human applications (≈ 4 min for a single slice), especially applications that require high resolution and/or large anatomical coverage. Translating SIR imaging to ultra-high field may allow for improved efficiency (27); however, ultra-high field scanners are not widely available in clinical settings. Previous work in rodent brains (28) has shown that large efficiency gains can be achieved by varying the predelay time (t_D), or time from the end of the FSE train to the next inversion pulse, in addition to varying t_i in the SIR-FSE sequence.

Here, we translate the more efficient variable- t_D approach into humans for the first time and show that, similar to work related to pulsed saturation imaging (22), additional gains in efficiency are possible in SIR imaging by fixing k_{mf} during the fitting process. This results in a model with four free parameters (PSR , R_{1f} , M_{0f} , and S_f), which can be estimated from images acquired at four optimized combinations of t_i and t_D . Fortunately, k_{mf} is often similar in normal and diseased neural tissue (29); therefore, we will show that assuming a constant k_{mf} during the fitting process does not significantly bias estimates of the other model parameters when optimal sampling strategies are employed. Toward this end, we first performed a series of numerical studies to determine optimal sampling strategies with respect to the precision and accuracy of parameter estimates (PSR , R_{1f} , M_{0f} , and S_f) for a given scan time. These optimized sampling strategies were then tested for validity in a series of bovine serum albumin (BSA) phantoms with different macromolecular contents and apparent T_1 values. Optimized SIR-FSE protocols were then deployed in the brains of healthy volunteers, and the resulting qMT parameters were compared to values obtained from previously published values (26). Finally, to demonstrate the applicability of our technique in neurodegenerative diseases, one patient with relapsing-remitting multiple sclerosis (RRMS) was studied.

THEORY

SIR-FSE Signal Equation

The SIR-FSE sequence (26) is an inversion recovery sequence that employs a low power inversion pulse followed by an FSE readout. The low power inversion pulse inverts the water proton longitudinal magnetization (M_{zf}) with minimal saturation of macromolecular proton longitudinal magnetization (M_{zm}), maximizing the difference between the pools and the sensitivity of the signal to MT. In addition to efficiently sampling k -space, the FSE train

allows one to assume that M_{zf} and M_{zm} are both nulled at the end of the readout (25). This occurs because *i*) the refocusing pulses in the FSE train invert any T_1 recovery of M_{zf} that occurs between pulses and *ii*) MT effectively pulls M_{zm} toward M_{zf} , nulling M_{zm} when the FSE train is sufficiently long (≈ 100 – 200 ms (25)). This assumption then allows one to account for a reduced t_D in the signal model, yielding significant gains in efficiency relative to traditional inversion recovery sequences that employ a $t_D \approx 5 * T_1$ to ensure full recovery prior to each inversion.

More formally, if we define the longitudinal magnetization vector $\mathbf{M}_z = [M_{zf} \ M_{zm}]^T$ and assume $\mathbf{M}_z(t_D=0) = \mathbf{0}$, the evolution of $\mathbf{M}_z$ can be described by (27)

$$\mathbf{M}_z(t_I, t_D) = \{\exp(\mathbf{A}t_I)\mathbf{S}[\mathbf{I} - \exp(\mathbf{A}t_D)] + [\mathbf{I} - \exp(\mathbf{A}t_I)]\}\mathbf{M}_0, \quad [1]$$

where $\mathbf{I}$ is the identity matrix, $\mathbf{M}_0 = [M_{0f} \ M_{0m}]^T$ is a vector of equilibrium magnetizations, $\mathbf{S} = \text{diag}(S_f, S_m)$ accounts for the effect of the inversion pulse on each pool ($S_f = -1$ indicates complete inversion of M_{zf} , $S_m = 1$ indicates no saturation of M_{zm}), and the matrix

$$\mathbf{A} = \begin{bmatrix} -(R_{1f} + k_{fm}) & k_{mf} \\ k_{fm} & -(R_{1m} + R_{mf}) \end{bmatrix} \quad [2]$$

defines the R_1 of each pool and the rate of MT exchange between pools. Because we only directly observed the water proton signal, the SIR-FSE signal model is defined by the M_{zf} component of Eq. [1], assuming $\mathbf{M}_0$ captures additional experimental scaling parameters (e.g., coil sensitivities, T_2 decay). This yields a model with seven independent parameters: R_{1m} , R_{1f} , S_m , S_f , M_{0f} , $PSR = M_{0m}/M_{0f}$, and k_{mf} . Consistent with previous work (25), S_m can be numerically estimated ($S_m = 0.83 \pm 0.07$ for a 1-ms block inversion pulse, Gaussian lineshape, and $T_{2m} = 10$ – 20 ms) and one can assume $R_{1m} = R_{1f}$ because the SIR signal is relatively insensitive to R_{1m} (28). With these assumptions, least squares fitting of SIR-FSE data with the M_{zf} component of Eq. [1] yields estimates of five independent model parameters: R_{1f} , S_f , M_{0f} , PSR , and k_{mf} . The dimensionality of the problem can be further reduced by assuming a k_{mf} value and holding it constant during fitting. In this case, estimates of four model parameters can be obtained: R_{1f} , S_f , M_{0f} , and PSR . In the following text, we refer to the model that includes k_{mf} as a free parameter as the *unconstrained* model, and the model with a fixed k_{mf} as the *constrained* models.

Cramér-Rao Lower Bound Theory

For a given set of SIR-FSE model parameters $\boldsymbol{\theta}$, the precision and accuracy of parameter estimates $\hat{\boldsymbol{\theta}}$ based upon these experimental observations depends on the chosen sampling scheme (t_I and t_D values) and analysis model (unconstrained or constrained k_{mf}). Cramér-Rao Lower Bound (CRLB) theory sets a lower limit on the uncertainty of $\hat{\boldsymbol{\theta}}$ and was used to evaluate both the sampling schemes and analysis model choices. We assume that SIR-FSE data are measured in the presence of Gaussian distributed noise with zero mean and a standard deviation (SD) of σ (see *Results* for numerical validation). In this case, the CRLB-

derived mean-squared error ($\text{MSE} = \text{bias}^2 + \text{variance}$) for a biased estimator can be calculated from (30,31)

$$\text{MSE}(\hat{\theta}_j) = b_j^2 + [(\mathbf{I} + \nabla \mathbf{b})\mathbf{F}^{-1}(\mathbf{I} + \nabla \mathbf{b})^T]_{jj}, \quad [3]$$

$b_j = E[\hat{\theta}_j] - \theta_j$ is the bias of the j^{th} parameter estimate, $\nabla \mathbf{b}$ is the gradient of these biases ($\mathbf{b}$) with respect to $\boldsymbol{\theta}$, $\mathbf{I}$ is the identity matrix, and $\mathbf{F}$ is the Fisher information matrix defined as

$$F_{jk} = \frac{1}{\sigma^2} \sum_{n=1}^N \left(\frac{\partial g_n}{\partial \theta_j} \frac{\partial g_n}{\partial \theta_k} \right). \quad [4]$$

Here σ is the standard deviation (SD) of the noise, g_n is the signal model evaluated at the n^{th} sampling point (the M_{zf} component of Eq. [1] evaluated at the n^{th} t_1 and t_D value), θ_j is the j^{th} model parameter, and θ_k is the k^{th} model parameter. For the constrained model, $\mathbf{b}$ and $\nabla \mathbf{b}$ can be numerically estimated by holding the constrained sample parameter (k_{mf}) constant while fitting noiseless synthetic data generated with varied model parameters (R_{1f} , S_f , M_{0f} , and PSR). For the unconstrained model, all the elements in $\mathbf{b}$ and $\nabla \mathbf{b}$ are zero and the MSE is defined solely by the variance of $\hat{\boldsymbol{\theta}}$. In this case, the MSE of $\hat{\boldsymbol{\theta}}$ can be calculated directly from the diagonal elements of the inverse of the Fisher information matrix, or $\text{MSE}(\hat{\theta}_j) = [\mathbf{F}^{-1}]_{jj}$.

METHODS

Optimization of SIR-FSE Sampling Schemes

As previously described (28), optimal SIR-FSE sampling schemes can be achieved for a range of tissue types (each with a unique set of model parameters) by minimizing the following CRLB-derived objective function:

$$\nu = \max_l \left\{ \sum_{j=1}^J \left(\frac{\text{MSE}(\hat{\theta}_{jl})}{\theta_{jl}^2} \right) \right\} \sum_{n=1}^N \left(t_{1,n} + t_{D,n} + t_{\text{FSE}} \right), \quad [5]$$

where l indexes a set of model parameters that characterize different tissue types, θ_{jl} is the j^{th} model parameter for the l^{th} tissue type, n indexes the sampling points, and t_{FSE} is the duration of the FSE train. The first term in Eq. [5] normalizes the MSE contribution from each parameter and selects the set of SIR parameters (or tissue type) representing the worst case, while the second term imposes a penalty for long t_1 and t_D values to improve efficiency. Thus, by finding t_1 and t_D values that minimize Eq. [5], the SNR efficiency for the worst combination of input parameters is maximized.

For the studies herein, optimizations were performed to find: 1) an optimal 5-point scheme for the unconstrained model (variable k_{mf}) and 2) an optimal 4-point scheme for the constrained model (fixed k_{mf}). For the latter, k_{mf} was fixed to the mean value reported in

healthy human brain at 3.0 T (12.5 s^{-1}) (26). Each optimization was performed over four tissue classes (see Table 1), covering the range of PSR , R_{1f} , and k_{mf} values observed in healthy and RRMS brains at 3.0 T (26). The remaining parameters did not significantly impact the optimization results and were, therefore, held constant across tissue classes ($S_m = 0.83$, $S_f = -1.0$, $M_{0f} = 1.0$, $t_{FSE} = 0.3 \text{ s}$, $R_{1m} = R_{1f}$, and $SNR = 200$ at thermal equilibrium (26)). Optimal sampling schemes were then determined by minimizing Eq. [5] via a global search (ga: genetic algorithm, MATLAB 2014b) followed by a local search (fmincon: sequential quadratic programming). A minimum $TR = t_1 + t_D + t_{FSE} = 0.8 \text{ s}$ was enforced during all optimizations to ensure specific absorption rate (SAR) limits were not exceeded. To minimize the impact of local minima, the entire search process was repeated 50 times with different random starting points, and the scheme with the minimum objective function across the 50 trials was selected as the optimal scheme.

Phantom Preparation

BSA (Sigma-Aldrich Corp., St. Louis, MO) phantoms of 5, 10, 15, and 20% were prepared in distilled water. Two additional phantoms of 10% and 15% BSA and 0.05 mM MnCl_2 were prepared to test the ability of each sampling scheme to separate MT and relaxation effects. All phantoms were cross-linked with 5% glutaraldehyde (Electron Microscopy Sciences, Ft. Washington, PA) at room temperature, immediately centrifuged for five minutes to remove bubbles, and stored at 4°C for at least 48 hours to allow the gel to set prior to MRI.

Subjects

Four healthy volunteers (25–27 y.o., 2 female) and one RRMS patient (37 y.o. female) received an MRI as part of this study. For the RRMS patient, diagnosis of disease status was made in the clinic prior to our examination. Our local institutional review board approved the study, and signed consent was obtained prior to all examinations.

Data Acquisition

Imaging was performed using a 3.0-T Philips Achieva whole-body MR scanner (Philips Healthcare, Best, The Netherlands). A two-channel body coil was used for transmission and a 32-channel head coil was used for signal reception. Single-slice SIR-FSE data were acquired in each volunteer (parallel to AC–PC line) and BSA phantom with i) the optimized 5-point scheme, ii) the optimized 4-point scheme, and iii) our previously published 16-point scheme (26) (15 t_1 values logarithmically spaced between 0.01–2.0 s and $t_1 = 10 \text{ s}$, constant $t_D = 2.5 \text{ s}$). Additional parameters for the human studies included: number of FSE lines/shot = 26, echo spacing = 5.9 ms, effective echo time (TE) = 80 ms, SENSE acceleration factor = 2.2, field-of-view = $216 \times 216 \text{ mm}$, acquired/reconstructed in-plane resolution = $2.0 \times 2.0 / 1.7 \times 1.7 \text{ mm}$, slice thickness = 5 mm, and two averaged signal acquisitions. This resulted in an acquisition time ≈ 4 minutes for a single slice using the 16-point scheme (the acquisition and t_1/t_D times for the optimized schemes are discussed in the *Results* section and in Table 2). Higher resolution SIR-FSE imaging was performed in the BSA phantoms (field-of-view = $112 \times 112 \text{ mm}$, acquired/reconstructed in-plane resolution = $1.0 \times 1.0 / 0.9 \times 0.9 \text{ mm}$) to ensure that each phantom contained an adequate number of voxels for data analysis.

In addition, slice thickness was increased to 20 mm to yield similar SNRs relative to the human studies.

Data Analysis

Data analyses were performed in MATLAB 2014b (Mathworks, Natick, MA). To estimate unconstrained model parameters (R_{1f} , S_f , M_{0f} , PSR , and k_{mf}), 16- and 5-point data were fit with the M_{zf} component of Eq. [1] (see the *SIR-FSE Signal Equation* section above for a brief description and (26,27) for additional details). Constrained model parameters (R_{1f} , S_f , M_{0f} , and PSR) were estimated from 4-point data in a similar fashion by fixing k_{mf} to 12.5 (26) and 35.0 s⁻¹ (28) for brain and BSA, respectively. Monte Carlo simulations (see Fig. 1) indicated that all sampling schemes uniquely converged to the correct solution over the range of expected tissue parameters in controls and RRMS patients.

For the phantom studies, each qMT parameter was evaluated in a central 9×9 voxel region-of-interest (ROI) within each phantom. For the human studies in healthy volunteers, ROIs were manually defined in the white matter and sub-cortical gray matter ROIs listed in Table 3 as described in (27). In the RRMS patient, ROIs were defined throughout normal-appearing white matter (NAWM) and in a lesion. Voxels near tissue/cerebrospinal fluid (CSF) boundaries were avoided to minimize the impact of partial-volume averaging. Mean ±SD parameter values were estimated for each ROI. To statistically test for differences in ROI parameter values between sampling schemes, non-parametric Wilcoxon signed rank tests were performed. Significance was defined at the $\alpha=0.01$ level to account for the effect of multiple comparisons. M_{0f} and S_f were excluded from these analyses because they include experimental scaling parameters and are not biologically relevant.

RESULTS

Numerical Studies

The optimization framework produced the sampling schemes listed in Table 2. The resulting 5- and 4-point schemes yielded 4.1- and 6.1-fold shorter scan times, respectively, relative to our previously published 16-point scheme. For each model parameter and sampling scheme, the mean (across tissues in Table 1) predicted SNR efficiency ($SNR/\sqrt{t_1 + t_D + t_{FSE}}$) was calculated using CRLB theory. Relative to the 16-point scheme, CRLB theory predicts a 1.4 and 1.8-fold increase in the SNR efficiency of PSR estimates from the 5- and 4-point schemes, respectively. For R_{1f} estimates, CRLB theory predicts a 1.5-fold increase in SNR efficiency from the 4-point scheme, and a 0.8-fold decrease in the SNR efficiency from the 5-point scheme.

To numerically validate the CRLB theory calculations upon which these schemes were derived, Monte Carlo (MC) simulations were performed. The RRMS lesion tissue class in Table 1 was selected for these simulations because it typically exhibited the largest bias for the constrained model (i.e., represented the worst-case scenario in Eq. [5]). For each simulation, synthetic data were generated using the sampling schemes in Table 2, Rician distributed noise was added with an SNR = 200 at thermal equilibrium, and the resulting noise-added data were fit as described above. This process was then repeated with 10,000

unique noise realizations to estimate the probability distribution function (PDF) of each SIR parameter. As shown in Figure 1, estimated parameter PDFs from CRLB theory and MC simulations agree for both the constrained (4-point, red) and unconstrained (5-point, blue) models. In other words, CRLB theory, which assumes Gaussian noise, accurately predicts the bias and variance of SIR parameters estimated in the presence of Rician noise (e.g., in magnitude MRI data (32)) and is a valid framework for the optimization proposed herein.

To provide further insight into the optimized sampling schemes, we estimated the normalized (per unit square root of scan-time) effect of each SIR parameter θ_l on the measured SIR signal M_{zf} as a function of t_I and t_D . More formally, we estimated each parameter's sensitivity efficiency

$$S_{\text{eff}}(t_I, t_D) = \frac{f M_{zf}}{f \theta_l} \frac{1}{\sqrt{t_I + t_D + t_{\text{FSE}}}}, \quad [6]$$

where S_{eff} is large for t_I - t_D values that enable precise and efficient parameter estimation—and small for t_I - t_D values that yield insensitivity to a given model parameter. In addition to providing insight into the optimized sampling schemes, the S_{eff} contours also provide guidance when the optimized schemes are not experimentally feasible. For example, the sample with the shortest t_D =10 ms may not be feasible due to experimental constraints (e.g., SAR). In this case, one can simply increase t_D ≈100 ms with minimal impact.

S_{eff} values estimated using sample parameters from white matter are given in the upper panel of Figure 2. The 5-point scheme can be seen to sample t_I - t_D regimes that maximize S_{eff} for each of the five parameters in the constrained model. Similarly, the 4-point scheme samples regimes that maximize S_{eff} for each of the four parameters in the constrained model, while avoiding the t_I - t_D regime that is most sensitive to k_{mf} . Previous work (25,33) has shown that the fast rate of the biexponential SIR signal is $\approx k_{\text{mf}}$. In this case, one expects the SIR signal to be sensitive to k_{mf} for short t_I values and independent of k_{mf} for long t_I values (i.e., after the fast-rate-component recovers), which is consistent with the findings in Figure 2. Fortunately, the SIR signal exhibits sensitivity to the other model parameters outside of the regime of k_{mf} sensitivity, allowing one fix k_{mf} without substantially reducing the precision or increasing the bias in the other parameter estimates.

This effect is quantified for the 4-point scheme in the bottom panel of Figure 2, where CRLB theory was used to estimate the root MSE (RMSE) and bias in PSR as a function of error in the assumed k_{mf} value. These simulations indicate that *i)* the bias in the estimated PSR is zero when k_{mf} is fixed to the true value (vertical dashed line, $k_{\text{mf}} = 12.5 \text{ s}^{-1}$) and increases with k_{mf} error, *ii)* the RMSE is relatively constant when the simulated tissue $k_{\text{mf}} \gtrsim 7.0 \text{ s}^{-1}$ due to the small contribution of bias to the RMSE, and *iii)* the relative bias is similar across all tissues in Table 1 (<10% when $k_{\text{mf}} > 6.0 \text{ s}^{-1}$).

Phantom Studies

Figure 3 shows PSR and R_{1f} maps from each BSA phantom (additional k_{mf}/S_f maps are given in Supporting Figure S1). Pair-wise comparisons (Wilcoxon signed rank tests)

between sampling schemes did not detect significant differences ($\alpha < 0.01$) for any scheme/parameter, suggesting that the optimized schemes yielded similar parameter estimates relative to the 16-point scheme. The estimated parameter SNR (mean/SD within each ROI) and SNR efficiency for each sample is given within the parentheses of Figure 3. For *PSR*, the 5- and 4-point schemes yielded parameter estimates with similar SNRs to the 16-point scheme, but with 4.1- and 6.1-fold shorter scan times, respectively. Across all samples, the measured SNR efficiency of *PSR* was 1.9/2.5-fold higher for the optimized 5/4-point schemes, which agreed with the predicted improvements from CRLB theory (2.2/2.1 for the 5/4-point schemes). Finally, *PSR* increased with BSA concentration only, while R_{1f} increased with both BSA and MnCl_2 concentrations (see columns three and five for samples with BSA+ MnCl_2). In other words, *PSR* separated MT and relaxation effects, while R_{1f} was unable to separate these effects.

Human Studies

Figures 4 and 5 shows parameter maps derived from each sampling scheme in a representative control and RRMS patient, respectively. These results are further quantified in Tables 3 and 4, which list mean ROI parameters in healthy controls and a patient with RRMS. Similar levels of precision (defined as the SD of the estimate) were obtained from all schemes, but with much shorter scan times for the optimized schemes. Unlike BSA, the optimized schemes in the brain yielded different estimates of *PSR* ($p=0.01$ for both optimized schemes) and R_{1f} ($p=0.01$ for both optimized schemes) relative to the 16-point scheme. As discussed below, these differences may be related to the variable t_D employed by the optimized schemes (see *Discussion*). Nevertheless, the optimized 4- and 5-point schemes yielded similar parameter estimates (mean relative difference of 4.7%/4.8% for *PSR*/ R_{1f}). In other words, although k_{mf} varied substantially across the brain (see Figure 6), a substantial portion of this variability can be attributed to the uncertainty inherent in estimating k_{mf} (28) and fixing k_{mf} in the 4-point scheme did not significantly alter parameter estimates relative to the 5-pt scheme. Furthermore, fixing k_{mf} reduced the sensitivity of *PSR* to partial-volume averaging (see Figure 4), yielding more consistent estimates across the entire slice.

DISCUSSION

We previously demonstrated (26) that SIR acquisitions yield parameters that are repeatable and sensitive to myelin/axon pathologies in patients with RRMS; however, these scans were of limited clinical value because they required four minutes for a single slice. The current study demonstrates for the first time that SIR parameters can be estimated within clinically acceptable acquisition times when t_D is varied, optimal t_1 – t_D combinations are selected, and/or k_{mf} is assumed. More specifically, we used CRLB theory to determine two novel optimal sampling schemes for the human brain at 3.0 T: *i*) a 5-point scheme (k_{mf} estimated from the data) and *ii*) a 4-point scheme (k_{mf} assumed). Both schemes offered significant improvements in precision efficiency (e.g., 4–6 fold for *PSR*) relative to our previously published scheme (26). These results were numerically validated via Monte Carlo simulations and experimentally validated in a series of BSA phantoms. Corresponding results in healthy subjects and a patient with RRMS demonstrated that the optimized schemes could be robustly translated into the human brain to provide quantitative

information on myelin content in 1 minute/slice. Fixing k_{mf} in the 4-point scheme also eliminated the influence of partial-volume averaging on estimates of PSR , which is especially important in regions near the ventricles or within smaller MS lesions (see Figure 5).

Previous studies in rodent brain at 7.0 T (28) showed similar efficiency gains could be achieved by varying t_D in SIR acquisitions. Herein, we translated and optimized this variable- t_D approach for human applications at 3.0 T for the first time and incorporated a novel data reduction strategy (fixing k_{mf}) to further reduce acquisition times. Although k_{mf} may be sensitive to the myelin lipid structure and chemical composition, k_{mf} values were similar in healthy subjects and patients with RRMS (Figure 6), which is consistent with previous findings (29). This allowed us to fix k_{mf} in the 4-point scheme without introducing systematic errors across cohorts. It should be noted that, although we repeated each optimization 50 times to minimize the impact of local minima, the final schemes might not represent the global minimum of the cost function in Eq. [5]. Furthermore, additional gains in efficiency may be possible by optimizing Eq. [5] for certain parameters (e.g., PSR), rather than giving equal weight to all model parameters. We did not employ the latter approach herein because it introduced large systematic errors in the other model parameters (28). Finally, the optimized schemes were designed for applications in the healthy and RRMS human brain at 3.0 T and would need to be tested, and potentially amended, for other applications and field strengths. Nevertheless, both optimized schemes are viable for future SIR studies in the human brain at 3.0 T, and the optimization framework developed herein can be readily applied to SIR applications in other tissues.

Previous qMT studies in humans have reported PSR values in the range of 10–16% and 3–8% for WM and GM structures, respectively (19,26,34–36). Reported MT rates have been less consistent; however, previous studies have typically reported k_{mf} values in the range of 10–40 s⁻¹. Although there have been few reports of R_{1f} , it can be shown that the observed T_1 reported in the literature is $\approx 1/R_{1f}$ when $R_{1m}=R_{1f}$ (27). Based upon this assumption, the mean observed T_1 across all schemes was 992±71 and 1352±74 ms for WM and GM structures, respectively. Thus, the parameters derived from all SIR sampling schemes (Table 3) were within the range of previously reported values in human brain at 3.0 T, although it should be noted that a portion of the observed variability across these previous studies may be attributed to differences in the model assumptions and acquisition strategies employed.

Experimental results in BSA phantoms (Figure 3) yielded consistent results across all sampling schemes. In other words, varying t_D and fixing k_{mf} did not introduce systematic errors in SIR parameter estimates in phantoms. In the brain, the optimized schemes also yielded consistent parameter estimates. Thus, like BSA, fixing k_{mf} did not introduce systematic errors into parameter estimates in the human brain. Unlike BSA, systematic differences were observed between the parameters (PSR and R_{1f}) estimated from the constant- and variable- t_D schemes in the brain. The reason for the discrepancy between the estimated parameters using the 16-point and the 5/4-point approaches is not clear, but there are several reasonable possibilities. For one, multi-exponential T_1 and T_2 relaxation has been reported in neural tissue due to the presence of water compartmentation (i.e., water between myelin bilayers and water within/between axons possess different MT/relaxation properties)

(37,38), which could yield parameter estimates that vary with t_1 and t_D when a single relaxation component is assumed. One could incorporate multiple relaxation components into the SIR model to account for this effect (39); however, this would result in a model with data acquisition/SNR requirements that preclude clinical implementation.

Another potential explanation for the observed differences between the constant- and variable- t_D approaches in the human brain is the effect of certain model assumptions ($S_m = 0.83$, $R_{1m}=R_{1f}$, and $M_z(t_D=0)=0$) on the estimated model parameters. For example, $M_z(t_D=0) = 0$ results in a signal offset whose relative contribution to the overall signal decreases with t_D . This effect was tested in our human white matter data by replacing the image with the shortest t_D in the optimized schemes ($t_1/t_D = 843/10$ ms for 5-point, $t_1/t_D = 1007/10$ ms for 4-point) with an image of similar t_1 (but longer t_D) from the 16-point scheme ($t_1/t_D = 938/2500$ ms). The resulting *PSR* estimates were nearly identical to the constant t_D scheme ($\approx 5\%$ relative difference). This suggests that incorrect assumptions in $M_z(t_D=0)$ may explain the observed differences between constant- and variable- t_D schemes, although the aforementioned contributions from multi-component relaxation and/or other parameters assumptions ($S_m = 0.83$, $R_{1m}=R_{1f}$) may also play a role. Together, these findings suggest that *i*) protocol normalization may be essential when comparing SIR parameter in the human brain across time/sites and *ii*) future work should focus on the influence of multi-exponential relaxation and model assumptions on estimated SIR parameters in neural tissue *in vivo*.

The fact that SIR does not require additional independent estimates (B_0 , B_1^+ , and T_1) results in simple data analysis pipelines that are readily amenable to neuroimaging applications, including those outside of the brain (e.g., spinal cord (29) and peripheral nerve (40)). In the past, long acquisition times and parameter estimation errors have been impediments to the clinical adoption of SIR. Compounding the long acquisition times, SIR is not directly amenable to multi-slice imaging because spins from neighboring slices would be *i*) inverted by the non-spatially-selective inversion pulse and/or *ii*) saturated (via MT effects) by the slice-selective refocusing pulses in the FSE readout. For the sake of discussion, assume we have ≈ 15 min to deploy a SIR acquisition in a clinical setting. Using our originally proposed 16-point scheme, only four slices could be collected in this time. In contrast, both optimized schemes would allow for near whole-brain coverage (16/24 slices for 5/4-point schemes) without sacrificing precision. In addition, the 4-point scheme has the significant benefit of avoiding misfits of *PSR* near ventricles.

Future work will investigate three-dimensional (3D) approaches with SENSE acceleration to achieve additional efficiency gains. In addition, alternate readouts (e.g., echo-planar imaging) will be investigated that may allow for reductions in TE and/or more efficient k -space coverage. This improved efficiency could be then traded for increased resolution, decreased scan time, and/or increased volumetric coverage.

CONCLUSIONS

This study demonstrates that SIR parameters can be estimated within clinically acceptable acquisition times when t_D is varied, optimal t_1 - t_D combinations are selected via CRLB

theory, and/or k_{mf} is assumed. The optimized protocols results were numerically validated via Monte Carlo simulations and experimentally validated in a series of BSA phantoms. Corresponding results in healthy subjects and a patient with RRMS demonstrated that the optimized schemes could be robustly translated into the human brain to provide quantitative information on myelin content. Future work includes further refinement and optimization of k -space coverage in SIR acquisitions to allow for increased volumetric coverage and comparison of results across a larger patient cohort.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

Comparison of SIR parameter PDFs from CRLB theory (lines) and Monte Carlo simulations (MC, diamonds). Shown are PDFs for PSR (a), R_{If} (b), and S_f values in RRMS lesions as defined in Table 1. In all cases, CRLB theory accurately captured the variance, or width in the PDF. In addition, CRLB accurately predicts bias, or shifts in the PDF relative to the true value (vertical gray lines), which results from fixing k_{mf} in the constrained model.

FIGURE 2.

(a) Simulated sensitivity efficiency (Eq. [6]) of each parameter in white matter as defined in Table 1. The contours encapsulate the 85th percentile of S_{eff} for each parameter. The 5-point scheme (black diamonds) samples t_1 - t_D regimes within the 85th percentile of S_{eff} for each of five model parameters. The 4-point scheme (white squares) samples regimes that maximize S_{eff} for each of four parameters (e.g., *PSR* in the red contour), while avoiding the k_{mf} -sensitive regime (blue contour). (b) Simulated RMSE (solid lines) and bias (dashed lines) in *PSR* for the 4-point scheme as a function of k_{mf} . RMSE and bias were normalized relative to *PSR*, yielding percent RMSE and bias values. Shown are the tissues classes yielding the

largest (worst case = RRMS lesions in Table 1) and smallest RMSE (best case = white matter I). The bias is zero when the fixed k_{mf} (vertical dashed line) matches the simulated values and increases with k_{mf} error; however, the RMSE is relatively constant when the simulated $k_{mf} \gtrsim 7.5s^{-1}$ due to the small contribution of bias to the RMSE.

FIGURE 3.

PSR and R_{1f} parameter maps from the center 9×9 voxels in each BSA/ MnCl_2 phantom (left-to-right) using each sampling scheme (top-to-bottom). The mean estimated parameter value for each sample is given in bold text, and the SNR/SNR efficiency is given within the parentheses. For the 4-point scheme, k_{mf} was fixed to 35.0 s^{-1} during fitting.

FIGURE 4.

Representative qMT parameter maps (left-to-right) from each sampling scheme (top-to-bottom) in a healthy subject. For the 4-point scheme, k_{mf} was fixed to 12.5 s^{-1} for all voxels during fitting, yielding a reduced sensitivity of PSR to partial-volume averaging near CSF/tissue boundaries (see outliers around the ventricles and in gray matter for the 16- and 5-point schemes).

FIGURE 5.

Parameter maps (left-to-right) from each sampling scheme (top-to-bottom) in a patient with RRMS. For the 4-point scheme, k_{mf} was fixed to 12.5 s^{-1} for all voxels during fitting. Note the reduction in PSR and R_{1f} in the lesion (gray arrow) of the RRMS patient.

FIGURE 6.

Whole-slice histograms of k_{mf} from the 16-point scheme. Shown are mean histograms across controls (red) and the histogram from one RRMS patient (blue). Similar distributions were observed across cohorts, both of which were centered near the fixed k_{mf} value (vertical dashed line) used for the constrained model.

TABLE 1

qMT parameters for the tissue classes used in the SIR-FSE optimizations. Values were chosen to cover the range of parameters observed in healthy and RRMS brains at 3.0 T. In white matter, two classes (I/II= maximum/mean observed PSR values) were defined to model the variation observed across different white matter structures. The remaining parameters were the same for all tissue classes: $S_m=0.83$, $S_f=-1.0$, $M_{0f}=1.0$, $t_{FSE}=0.3$ s, $R_{1m}=R_{1f}$, and SNR=200 at thermal equilibrium.

Tissue	PSR (%)	k_{mf} (s ⁻¹)	R_{1f} (s ⁻¹)
White Matter I	20	5	1.5
White Mater II	12	10	1.0
Gray Matter	8	15	0.7
RRMS Lesion	5	20	0.5

TABLE 2

Optimized SIR sampling schemes. Shown are optimal 5-point (unconstrained model) and 4-point (constrained model, fixed $k_{mf} = 12.5 \text{ s}^{-1}$) schemes for the tissue classes in Table 1.

5-point		4-point	
t_I (ms)	t_D (ms)	t_I (ms)	t_D (ms)
10	3270	10	684
50	4489	10	4171
56	1652	278	2730
277	2922	1007	10
843	10	-	-

SIR parameter values in different healthy white/gray matter structures. Shown are mean $\pm$ SD values across four healthy control subjects for each sampling scheme. For the 4-point scheme, k_{mf} was fixed to 12.5 s^{-1} .

TABLE 3

	PSR (%)			R_{lr} (s^{-1})			k_{mf} (s^{-1})		
	16-pt	5-pt	4-pt	16-pt	5-pt	4-pt	16-pt	5-pt	4-pt
<i>Genu</i>	12.8 $\pm$ 1.1	15.6 $\pm$ 1.5	15.4 $\pm$ 1.5	1.15 $\pm$ 0.10	1.11 $\pm$ 0.09	1.02 $\pm$ 0.05	13.4 $\pm$ 3.4	12.1 $\pm$ 2.4	
<i>Splenium</i>	10.3 $\pm$ 0.8	13.6 $\pm$ 1.3	13.2 $\pm$ 1.0	1.04 $\pm$ 0.08	1.00 $\pm$ 0.07	0.96 $\pm$ 0.07	11.7 $\pm$ 2.2	9.8 $\pm$ 0.7	
<i>Internal capsule</i>	8.4 $\pm$ 0.6	11.3 $\pm$ 0.2	10.8 $\pm$ 0.3	0.97 $\pm$ 0.01	0.92 $\pm$ 0.02	0.87 $\pm$ 0.01	10.6 $\pm$ 0.8	9.6 $\pm$ 1.3	
<i>Frontal WM</i>	12.2 $\pm$ 1.1	14.4 $\pm$ 0.7	14.8 $\pm$ 0.6	1.08 $\pm$ 0.03	1.05 $\pm$ 0.02	1.01 $\pm$ 0.03	11.2 $\pm$ 1.0	10.4 $\pm$ 0.4	
<i>Occipital WM</i>	10.5 $\pm$ 0.3	12.8 $\pm$ 0.1	12.7 $\pm$ 0.3	1.05 $\pm$ 0.03	1.01 $\pm$ 0.02	0.96 $\pm$ 0.03	10.0 $\pm$ 0.3	9.5 $\pm$ 0.6	
<i>Putamen</i>	5.0 $\pm$ 0.5	6.4 $\pm$ 0.4	6.4 $\pm$ 0.9	0.78 $\pm$ 0.02	0.77 $\pm$ 0.02	0.75 $\pm$ 0.05	23.8 $\pm$ 6.7	18.3 $\pm$ 1.7	
<i>Head of caudate</i>	4.5 $\pm$ 0.3	5.6 $\pm$ 0.4	4.8 $\pm$ 0.5	0.72 $\pm$ 0.02	0.71 $\pm$ 0.01	0.65 $\pm$ 0.02	27.9 $\pm$ 2.7	17.5 $\pm$ 2.7	
<i>Thalamus</i>	5.4 $\pm$ 0.4	7.6 $\pm$ 0.2	6.5 $\pm$ 0.5	0.78 $\pm$ 0.02	0.75 $\pm$ 0.02	0.73 $\pm$ 0.01	18.6 $\pm$ 2.1	15.9 $\pm$ 0.7	

SIR parameter values in from NAWM and lesions in a patient with RRMS. Shown are mean $\pm$ SD values across each ROI. For the 4-point scheme, k_{mf} was fixed to 12.5 s⁻¹. The elevated k_{mf} values from the 16-point lesion ROI can be attributed to partial-volume averaging with edematous tissue (see the lesion in Figure 5).

TABLE 4

	PSR (%)			$R_{1\rho}$ (s ⁻¹)			k_{mf} (s ⁻¹)		
	16-pt	5-pt	4-pt	16-pt	5-pt	4-pt	16-pt	5-pt	4-pt
NAWM	9.8 $\pm$ 1.9	12.1 $\pm$ 2.3	12.0 $\pm$ 2.2	0.98 $\pm$ 0.09	0.95 $\pm$ 0.08	0.90 $\pm$ 0.07	10.5 $\pm$ 3.4	10.6 $\pm$ 3.2	
Lesion	2.1 $\pm$ 0.4	3.4 $\pm$ 0.5	2.6 $\pm$ 0.6	0.50 $\pm$ 0.03	0.48 $\pm$ 0.04	0.47 $\pm$ 0.04	36.3 $\pm$ 21.8	7.5 $\pm$ 2.7	