Myelin water fraction mapping from multiple echo spin echoes and an independent $B_1^+$ map

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Purpose: Myelin water fraction (MWF) is often obtained from a multiple echo spin echo (MESE) sequence using multi-component $T_2$ fitting with non-negative least squares. This process fits many unknowns including $B_1^+$ to produce a $T_2$ spectrum for each voxel. Presented is an alternative using a rapid $B_1^+$ mapping sequence to supply $B_1^+$ for the MWF fitting procedure.

Methods: Effects of $B_1^+$ errors on MWF calculations were modeled for 2D and 3D MESE using Bloch and extended phase graph simulations, respectively. Variations in SNR and relative refocusing widths were tested. Human brain experiments at 3 T used 2D MESE and an independent $B_1^+$ map. MWF maps were produced with the standard approach and with the use of the independent $B_1^+$ map. Differences in $B_1^+$ and mean MWF in specific brain regions were compared.

Results: For 2D MESE, MWF with the standard method was strongly affected by $B_1^+$ misestimations arising from limited SNR and response asymmetry around 180°, which decreased with increasing relative refocusing width. Using an independent $B_1^+$ map increased mean MWF and decreased coefficient of variation. Notable differences in vivo in 2D MESE were in areas of high $B_1^+$ such as thalamus and splenium where mean MWF increased by 88% and 31%, respectively ($P < 0.001$). Simulations also demonstrated the advantages of this approach for 3D MESE when SNR is <500.

Conclusion: For 2D MESE, because of increased complexity of decay curves and limited SNR, supplying $B_1^+$ improves MWF results in peripheral and central brain regions where flip angles differ substantially from 180°.

Keywords
flip angle estimation, multi-component $T_2$ fitting, myelin water fraction, stimulated echoes

1 | INTRODUCTION

Transverse relaxation ($T_2$) mapping is commonly performed with a multiple echo spin echo (MESE) technique, though other methods are possible. As shown by MacKay,1 multiple component analysis of the transverse decay in vivo brain can yield the myelin water fraction (MWF), identified as the proportion of the short $T_2$ component in the tissue.
the voxel. Use of this method is widespread and has particular application to multiple sclerosis, a demyelinating disease. Spectrum analysis of the $T_2$ decay data provides underlying water compartments, including myelin water and intra-/extracellular water. The $MWF$ increases the specificity of $T_2$ mapping to myelin, although other short $T_2$ species may serve as a confound.

Perfect $180^\circ$ refocusing in MESE sequences is required to generate an exclusively $T_2$ modulated signal decay. In practice, the theoretical refocusing stipulation is violated because of: imperfect refocusing profiles, transmit calibration errors, and radio frequency (RF) interference effects, which all collude to alter the range of refocusing angles across the volume of interest. Hence, mono- or multi-exponential fittings of the corresponding $T_2$ times need to account for such effects.

Recent literature for $MWF$ estimation from a MESE sequence includes stimulated echo compensation and uses a multi-exponential fit with a regularized non-negative least squares (NNLS) algorithm to decompose decay curves into $T_2$ distributions with no prior assumption about the number of contributing $T_2$ components. However, the fitting requires knowledge of the transmit RF field ($B_1^+$) in each voxel that modulates the nominal angles prescribed. Therefore, to produce proper dictionary matrices for the NNLS process, it is common practice to perform a $B_1^+$ optimization step to estimate the apparent $B_1^+$ of the decay curve. However, estimation of the $B_1^+$ parameter from the echo train is complicated by oscillating behavior of stimulated echoes and noise and could lead to increased susceptibility of NNLS fit results to noise.

Modeling of the MESE signal decay may be performed in many ways including using the extended phase graph (EPG) algorithm, which computes multi-echo signal decay curves given $T_1$, $T_2$, inter-echo spacing time, and the corresponding refocusing angle. This EPG method is used in current regularized NNLS fitting algorithms designed particularly for 3D MESE experiments that can be modeled by a single flip angle in each voxel and have symmetry around a refocusing angle of $180^\circ$. However, for slice selective RF pulses, the analysis is more complex, requiring accounting for RF slice profile effects. Particularly for 2D slice selective MESE sequences, Bloch modeling is needed to exactly account for RF pulse profile effects across the voxel. For example, recent work using single component $T_2$ fitting of a 2D MESE sequence demonstrated different fitting results for $B_1^+$ and $T_2$ depending on how the RF pulses were simulated. In particular, flip angle errors were substantial when estimating the flip angle from the decay curve train using EPG methods without Bloch modeling of the RF profiles. Furthermore, even when using Bloch modeling, the flip angle estimate was not in exact agreement with the measured angle, because of multiple possible similar solutions and the presence of noise. Akhondi-Asl and colleagues have recently demonstrated $MWF$ mapping from 2D MESE using full Bloch modeling to more precisely model the signal decay. However, this method still estimates the $B_1^+$ from the 2D MESE echo train to obtain the apparent $B_1^+$ value and any $B_1^+$ misestimations may affect the $MWF$ estimation.

Here, we investigated whether supplying the $B_1^+$ values to the fitting process, via an independent $B_1^+$ map, would increase the precision of $MWF$ estimations compared to the standard approach of using the apparent $B_1^+$ via an optimization step derived from the MESE echo train. This new approach for $MWF$ estimation eliminates the extra $B_1^+$ optimization step, but requires a $B_1^+$ map that has proven successful for single component $T_2$ mapping.

We investigated the value of this approach for $MWF$ estimation in simulations of 2D and 3D MESE sequences and in vivo human brain experiments with 2D MESE.

## METHODS

### Simulation of $T_2$ decay data

Visible water compartments in the brain water pool can be categorized into 3 environments: myelin water (MW), intra-extra cellular water (IEW), and cerebrospinal fluid. We defined a model for simulations, which only consists of MW ($T_2 = 15$ ms, $T_1 = 600$ ms) and IEW ($T_2 = 75$ ms, $T_1 = 1000$ ms) environments, corresponding to healthy white matter (WM).

Using this model, simulated $T_2$ decays were created, with an extra step to calculate Rician noise effects. Note that because the echo train decays to near 0, Rician noise was used rather than Gaussian. For simulation of 3D MESE data with nonselective refocusing pulses the EPG algorithm was used; however, for 2D MESE data generation full Bloch modeling was incorporated to account for the slice profile across the voxel.

The $T_2$ distributions for each water compartment are generated using a truncated Gaussian distribution with a SD of 10% of the mean and were truncated to 0 for values farther than 2 SDs from the mean. We defined the signal-to-noise ratio (SNR) as:

$$\text{SNR} = \frac{\text{max}(S(t))}{\sigma}$$

where $\sigma$ is the standard deviation of the Rician noise and $S(t)$ is the decay signal available at each time $t$ in the echo train. Note that the maximum signal is not necessarily at the first echo due to stimulated echo contributions. All the simulations used 32 echoes and 10 ms inter-echo spacing.
experiments. For 3D, nonselective refocusing pulses were assumed.

2.2 Analysis and $T_2$ distribution process

The 3D MESE data (simulation only) were analyzed on a voxel-based approach using the regularized NNLS algorithm with stimulated echo estimation (https://mriresearch.med.ubc.ca/news-projects/myelin-water-fraction/). This method uses the standard model for $T_2$ analyses, which does not make any priori assumptions about the distribution of signal decay.

Set parameters included 60 logarithmically spaced $T_2$ times, and $T_2$ range from 8 ms to 2 s with the lower limit slightly smaller than echo-spacing to better capture the MW peak. A constant $T_1$ value (= 1 s) is used for all decay curves and voxels because it has been shown to have negligible error. The refocusing flip angle experienced by the voxel needs to be set or apparent values need to be estimated.

For 2D MESE data (simulation and in vivo data), the fitting procedure used the same regularized NNLS algorithm discussed above for 3D data; however, decay curve generation required a different approach because of the slice profile effects across each voxel. The pulse sequence train was simulated to produce decay curves from a protocol file containing exact timings, gradient, and RF field that was then fed into the Bloch simulator code project (http://www-mrsrl.stanford.edu/~brian/blochsim/) that provides the magnetization vector at each given time and point in space. The code used 513 equally spaced points across 3x the slice-thickness. The 2D signal decay curve generation was handled using in-house wrapper code by summation of magnetizations across the slice profile at each required echo time point. The same range of $T_2$ values as 3D was used to generate dictionary matrices.

As per common practice, a regularization term was added for the NNLS fitting, so that there would be an ~2% increase in the sum of the squared residual of the fitted curve. Finally, after acquiring the solution, myelin water fraction was determined by applying a $T_2$ threshold value of 40 ms.

2.3 $B_1^+$ estimation

Typically, several linearly spaced $B_1^+$ values (for 3D, usually 8 flip angles ranging from 100° to 180°) are tested to enable $B_1^+$ estimation from NNLS solutions. Next, by back projecting the solution and comparing to the experimental decay curve, the sum of squares measure of residuals or $\chi^2$ is computed. Finally, $\chi^2$ values versus $B_1^+$ is fed to a cubic spline function to interpolate the 8 data point curve. The assumption is that the true $B_1^+$ would produce the smallest $\chi^2$, therefore, by finding the $B_1^+$ that corresponds to minimum $\chi^2$, the $B_1^+$ estimate or apparent $B_1^+$ value is obtained to use for generating the basis decay curves for the regularized NNLS process. This process is usually done for 3D data, but for 2D data a similar procedure is performed with the difference that the grid search for the correct $B_1^+$ is done over the entire range used in the lookup table (here, we used 1401 data points ranging from 0.5-1.5 in steps of 0.001) instead of using limited data points across the range.

The difference in the $B_1^+$ estimation process for 2D and 3D MESE relates to the greater complexity of 2D MESE curves that arises from the slice profile and the resulting asymmetry of 2D MESE decay around $B_1^+$ value of 1 (flip angle of 180°), which adds to the complexity of estimation.

2.4 Numerical simulations

The effect of $B_1^+$ miscalculation was considered by varying the error in the fitted $B_1^+$ from -0.3 to +0.3 using 0.01 increments. The $B_1^+$ range was 0.6 to 1.4 for 2D data, whereas for 3D data, $B_1^+$ did not exceed 1.0 because the EPG outcome is symmetric around 1.0 (i.e., $B_1^+$ of 1.1 results in the same decay curve as 0.9). The fractions for water compartments were 85% IEW (mean $T_2 = 75$ ms, SD = 7.5 ms), and 15% MW (mean $T_2 = 15$ ms, SD = 1.5 ms). The procedure at each $B_1^+$ value was repeated 500 times (SNR of 200) with the aforementioned simulation relaxation parameters to calculate the mean of MWF estimations. The mean MWF estimation versus $B_1^+$ difference from ground truth was examined.

To compare the precision of the multi-component fit of the 2 approaches, the coefficient of variance (CoV%) of the MWF estimation at different SNR values ranging from 50 to 1000 in increments of 50 was calculated using the same water compartment values as above. The procedure was repeated 1000 times at each $B_1^+$ value (ranging from 0.7 to 1.3 using 0.05 step size).

To address the effect of different slice profiles, we simulated a range of refocusing to excitation slice-thickness ratios (relative refocusing width ranging from 1 to 4) using the standard unmodulated Hanning filtered sinc RF refocusing pulses of 2.9 ms duration. We also simulated a tailored low specific absorption rate (SAR) variable-rate selective excitation (VERSE) pulse (3.84 ms length time) with 1.2 relative refocusing width. We used the same parameters mentioned above using 500 realizations of noise to calculate CoV% of MWF estimations using the 2 methods.
2.5 In vivo experiments

Human brain data were acquired from 5 healthy volunteers (22-42 years old) at 3 T (Prisma, Siemens Healthcare, Erlangen, Germany) using a 64-channel head coil. All subjects provided informed consent and this study was approved by the University Ethics Board. A 32 echo 2D MESE sequence was used for T2 measurement (TE/ΔTE/TR = 10/10/1000 ms, 4 slices, unmodulated Hanning-windowed sinc shaped refocusing pulses with 2.9 ms duration, refocusing/excitation slice-thickness factor 1.2, in-plane resolution 1.2×1.3 mm, slice thickness 5 mm, slice gap 200%, 3 averages, and acquisition time 12 min and 14 s). A 3D T1 weighted MPRAGE sequence was collected for region segmentation (1 mm isotropic resolution, 3.6 min). A Bloch-Siegert flip angle mapping sequence was used to spatial resolution 1.25×1.25×3.0 mm3 and 37 s acquisition time. Images were registered using the SPM12 MATLAB toolbox (The MathWorks, Natick, MA).

Images were analyzed to produce MWF maps using the aforementioned processes. Comparisons were made between the standard approach using the apparent B1+ from the echo train, and the new method that uses a supplied B1+ map. MWF maps were compared using manually segmented regions of interest (ROI) and the scatter plots of all voxels in the central slices. Plots compared the supplied to the apparent B1+ values and the difference of MWF values estimated by the 2 methods. The ROIs were performed in 3 WM areas (frontal WM, genu, splenium, and forceps major) and 2 deep gray matter territories (thalamus, caudate). A student t test was used to reject the null hypothesis of equal mean MWF in each ROI. MWF differences of the 2 methods were also compared to the ground truth B1+ values.

3 RESULTS

Figure 1 shows the signal responses generated from the Bloch simulation of the 2D MESE sequence using a Hanning-windowed sinc pulse (as used in in vivo experiments) (Figure 1A,C) and a low SAR VERSE pulse (Figure 1C,D). The magnitude signal response profiles and decay curves show a larger second echo owing to the recovery of stimulated echoes, despite the fact that both refocusing pulses are identical. The slice response profiles of the tailored low SAR pulse are somewhat wider. These normalized 2D MESE decay curves lack symmetry around B1+ of 1 as previously recognized, although there is much similarity between them. Histograms of the flip angle and apparent B1+ results for 3D and 2D simulations are shown in (Figure 1E-H). For 2D MESE data (Figure 1E,F), 2 distinct peaks are evident, with approximate symmetry around B1+ of 1.0 and the smaller peak shrinking as SNR increases. The 3D MESE data estimation results (Figure 1G,H) show poorer results for the larger flip angle at smaller SNR values with the probability of miscalculating the flip angle to 180° rising as the SNR decreases and also when the actual flip angle gets closer to the upper boundary.

Figure 2 illustrates the effect of having a bias in the B1+ parameter (B1+ error) and the effects of SNR on MWF when using an MWF of 15% for 2D and 3D MESE. For the 3D MESE data (Figure 2A), only B1+ values less than 1.0 are shown because of exact symmetry around 1.0. In contrast, for 2D MESE (Figure 2B), the B1+ values greater than 1.0 do not generate symmetrical values, although they are similar with an opposite slope. The effect of SNR on the CoV% of the MWF estimation is shown in (Figure 2C-E). Supplying the B1+ values for 2D and 3D MESE data yields improvements with the 2D MESE data showing the greatest differences. Importantly, the supplied B1+ method performs similarly for different B1+ values, whereas the apparent B1+ method is quite dependent on this variable. Figure 2E shows the results of RF pulse alterations, demonstrating that increasing the refocusing to excitation thickness ratio in 2D MESE reduces the difference between the 2 methods. In addition, the RF pulse type affects results with the low SAR pulse showing the largest difference between methods. The general pattern of improvement is observed when supplying the B1+ parameter in all cases, with greatest effects in 2D MESE.

A typical example of apparent and supplied B1+ maps and resulting MWF is shown in Figure 3. Most of the apparent B1+ values are close to 1.0 with clear underestimation in central regions where the supplied map is >1.0. The 2 methods yield similar MWF maps; however, there are local differences that are pointed out by the arrows, which are in alignment with the local misestimations in the B1+ maps and the difference MWF map. Generally, the local errors caused by the misestimations in the apparent B1+ when using the signal decay optimization step resulted in underestimated MWF values.

The in vivo ROI analysis of MWF maps in Table 1 illustrates mean MWF values are elevated when using the proposed method (except for genu of corpus callosum where there is no difference). The linear correlation between the 2 approaches was generally high; however, in regions where supplied B1+ values were much greater than 1.0 (splenium of corpus callosum and thalamus), the correlation coefficient is reduced (0.8 and 0.7). Other ROIs show high linear correlation values (>0.9) and the mean B1+ observed in these territories was close to 1.0. Generally, the CoV% (intra-subject) of mean MWF values decreases using
Figure 1 RF pulse and signal decay simulations for 2D MESE are shown along with simulated $B_1^+$ histograms for 2D and 3D MESE sequences. Bloch simulation results for 2D MESE used a standard Hanning-windowed sinc pulse (A,C) or a low SAR VERSE pulse (B,D) both with a refocusing to excitation thickness factor of 1.2. Magnitude signal response across the slice profile for excitation and the first 2 echoes are shown (A,B) along with normalized 2D MESE simulated signal decay curves using $T_2$ of 75 ms (C,D). Note the similar decay curves for disparate $B_1^+$ values. Histograms of apparent $B_1^+$ results from the optimization step at 3 SNR levels (100, 200, and 500) for 2D and 3D MESE simulations using MWF of 15% and standard RF parameters are shown in (E-H). Histograms for 2D MESE data are shown where the ground truth is $B_1^+$ of 0.8 in (E) and $B_1^+$ of 1.1 in (F). 3D MESE results are shown when the actual flip angle was (G) 150°, and (H) 170°. For 2D MESE, variations may occur even at SNR of 500, owing to similar solutions on either side of $B_1^+$ of 1.0. In contrast, 3D results are more focused owing to exact symmetry in the signal response on either side of 180° because of only a single flip angle value affecting the whole voxel
FIGURE 2  Effect of $B_1^+$ error (A,B) and SNR (C-E) on MWF estimations using 15% MWF. The effect of $B_1^+$ error on the MWF estimation is simulated with an SNR of 200 and a nominal angle of 180° using (A) 3D nonselective refocusing, and (B) 2D slice selective MESE with standard RF parameters (1.2 relative refocusing width, Hanning windowed sinc). The effect of SNR on MWF coefficient of variation (CoV%) is illustrated for a range of $B_1^+$ values and relative refocusing widths. (C) 2D MESE using the refocusing to excitation ratio of 1.2, (D) 3D MESE simulations with nonselective refocusing, and (E) 2D MESE using a range of refocusing to excitation ratios for the standard RF pulse and a low SAR VERSE pulse with thickness ratio of 1.2. MWF CoV% is shown in blue for the apparent $B_1^+$ method and red for the supplied $B_1^+$. 1000 different Rician noise realizations were used in each case. For 3D MESE $B_1^+$, only values <1.0 are plotted as curves are symmetrical around this value (analogous to flip angle of 180°). In (E), the letter “S” indicates the supplied $B_1^+$ method and a range of $B_1^+$ values (from 0.6 to 1.4) were used to calculate the average values at each relative refocusing width.
FIGURE 3 $B_1^+$ mapping and MWF maps from 1 subject. The apparent $B_1^+$ from the decay train optimization step (top row) and the supplied $B_1^+$ maps (second row) are shown, along with the difference image (third row). In particular, the apparent $B_1^+$ from the decay train underestimates high $B_1^+$ found in central regions and extending to the posterior periphery in this subject. MWF maps are shown using apparent $B_1^+$ values (fourth row), supplied $B_1^+$ values from the independent $B_1^+$ map (fifth row), and the difference map of the 2 (bottom row). Four slices from a single subject are shown. Purple arrows point to areas with visible MWF improvements when supplying the $B_1^+$ values.
TABLE 1  Mean and standard deviation of MWF values across all subjects

| Region of interest | MWF (%) from apparent $B_1^+$ (mean; SD) | MWF (%) from supplied $B_1^+$ (mean; SD) | $P$-value ($t$ test)* | Correlation coefficienta  | Supplied $B_1^+$ values (mean; SD) |
|--------------------|------------------------------------------|------------------------------------------|----------------------|---------------------------|-----------------------------------|
| Splenium           | 14.0; 3.5                                | 18.3; 3.1                                | 1.2 × $10^{-6}$      | 0.80                      | 1.13; 0.03                        |
| Genu               | 13.7; 3.7                                | 13.7; 3.7                                | 0.9                  | 1.00                      | 0.98; 0.03                        |
| Caudate            | 4.8; 1.8                                 | 6.2; 1.9                                 | 2.1 × $10^{-6}$      | 0.91                      | 1.05; 0.03                        |
| Thalamus           | 5.9; 1.2                                 | 11.1; 1.1                                | 2.0 × $10^{-6}$      | 0.70                      | 1.15; 0.03                        |
| Frontal WM         | 12.3; 1.6                                | 12.9; 1.6                                | 5.8 × $10^{-6}$      | 0.99                      | 0.93; 0.02                        |
| Entire WM          | 12.2; 1.4                                | 13.2; 1.2                                | 1.6 × $10^{-6}$      | 0.98                      | 0.98; 0.03                        |

*aThe linear correlation coefficient of the mean MWF between the 2 methods.

*P*-values show the significance of the mean MWF difference when comparing the 2 methods.

FIGURE 4  Scatter plots from in vivo experiments showing relationships between the MWF difference (supplied $B_1^+$ minus apparent $B_1^+$) and the $B_1^+$ values. (A,B) MWF difference versus the supplied $B_1^+$ values is shown for 2 subjects. Differences between methods increase when the supplied $B_1^+$ differs from 1.0, corresponding to 180° refocusing in these experiments. (C) Scatter plots of the apparent $B_1^+$ values versus supplied $B_1^+$ values from all subjects. (D) MWF difference versus the $B_1^+$ difference (supplied values minus the apparent values) from all subjects. In all cases, all voxels within white matter from 3 central slices were included.
the proposed method (up to ~50% decrease depending on region).

Figure 4A,B shows in vivo scatter plots comparing supplied B\textsuperscript{1+} values and the MWF difference of the 2 methods for all WM voxels in central slices. Methods perform similarly at B\textsuperscript{1+} of 1.0 with larger MWF differences further from this value. Figure 4C shows the relationship between apparent B\textsuperscript{1+} and supplied B\textsubscript{1+} for all subjects. Values near 1.0 tend to be estimated as 1.0, and generally, values under 1.0 get overestimated and values over 1.0 get severely underestimated. The relationship of MWF difference of the 2 methods compared to the difference of the B\textsuperscript{1+} values used in the fitting process is depicted in Figure 4D. The underestimation of apparent B\textsuperscript{1+} when the supplied B\textsuperscript{1+} is >1.0, leads to underestimation of MWF, showing a similar pattern of negative bias in the MWF estimation as seen in Figure 2 for the special case of 15% MWF. The differences observed between the 2 figures are because of the constant value for MWF used in simulation, whereas in the in vivo experiments have a range of different MWF values contributing.

4 | DISCUSSION

The effects of B\textsuperscript{1+} error on MWF using regularized NNLS fitting were examined for 2D and 3D MESE and the feasibility of B\textsuperscript{1+} optimization supplied through an independent B\textsuperscript{1+} map was explored. Simulations showed biases in the optimization step can arise as SNR is reduced from ideal levels, especially in 2D MESE data where 2 distinct peaks appear in the B\textsuperscript{1+} histograms on opposing sides of B\textsuperscript{1+} = 1.0. The presence of the 2 peaks arises because of similar, but not exact decay curves around B\textsuperscript{1+} = 1.0 and the presence of noise might alter the estimation result to the wrong side, as previously seen in single component T\textsubscript{2} analysis. The optimization step tries to acquire the smallest residual, over-fitting the noise (and artifacts) in the decay data. The scope of the B\textsuperscript{1+} misestimations in the apparent B\textsuperscript{1+} is more impactful for 2D MESE compared to 3D MESE. Increasing the relative refocusing to excitation width ratio improves 2D MESE results and large ratios, although impractical for multi-slice experiments, approach 3D MESE results.

For in vivo 2D MESE experiments, the use of the B\textsuperscript{1+} optimization step resulted in most central values in the apparent B\textsuperscript{1+} maps being near 1.0, which aligns with previous literature. The estimations were mostly <1.05, which Akhondi-Asl et al. used for the maximum value in their plots. When comparing the apparent B\textsuperscript{1+} map to the supplied B\textsuperscript{1+} map, large underestimations were observed where actual B\textsuperscript{1+} >1.05, resulting in significant MWF underestimations.

MWF differences between using a supplied B\textsuperscript{1+} map and the apparent B\textsuperscript{1+} map from the standard decay train estimation have a strong spatial dependence on the B\textsuperscript{1+} pattern. MWF values across the entire WM, have a strong correlation (0.98, P < 0.001) between the 2 methods; however, local regions can differ substantially depending on B\textsuperscript{1+} misestimation errors. In particular, differences in the MWF estimations in areas with B\textsuperscript{1+} >1.05 were ~0.04, which is a large error considering the average MWF in WM was ~0.13.

In a recent study by Lankford and Does, constraining the flip angle was examined theoretically for single component T\textsubscript{2} fitting demonstrating analytically how bias in the flip angle estimation propagates to bias in T\textsubscript{2} estimates. In another study by Wiggermann et al. detailed examination of B\textsuperscript{1+} inhomogeneity and SNR was performed for multi-component myelin water calculations using 3D MESE (with nonselective refocusing). Our work extends from these works by examining MWF in 2D MESE sequences, while also including 3D MESE simulations for comparison. We found the value of an independent B\textsuperscript{1+} map was minimal for 3D MESE when SNR >500, which is in alignment with Wiggermann et al.

For 2D MESE acquisitions, the slice profile gives rise to a range of flip angles across each voxel, therefore, either the Bloch equations need to be solved or EPG decay profiles need to be integrated across the slice. This increased complexity makes the results strongly affected by the B\textsuperscript{1+} field and without exact symmetry around B\textsuperscript{1+} = 1.0. Even for single component T\textsubscript{2} fitting of 2D MESE, which has only 3 unknowns per voxel, previous work has shown how B\textsuperscript{1+} misestimations from the decay curve may occur because of the lack of symmetry leading to T\textsubscript{2} errors that are improved by supplying a B\textsuperscript{1+} map. Previous work on 2D MESE multi-component T\textsubscript{2} analysis using Bloch or EPG approaches showed plausible and reproducible results for MWF maps, but the effects of B\textsuperscript{1+} estimation were not examined thoroughly.

The 2D MESE sequences tend to have lower SNR levels than 3D (~300 in our experiments), which are under the sufficient values suggested for ideal MWI analysis (>700), therefore, a compromise on ideal SNR is needed for 2D MESE work, which then points to the value of an independent B\textsuperscript{1+} map. For 3D MESE methods, a higher SNR threshold is possible, but recent work with 3D GRASE has lower SNR (150-300 range). The high SNR requirement (700) for multi-component T\textsubscript{2} analysis of 3D MESE data is considered too strict in recent literature.

Prospective studies could include a rapid B\textsuperscript{1+} map, requiring only a small fraction of the time necessary for an MWI acquisition. Here, we used the Bloch-Siegert approach for supplying B\textsuperscript{1+} values, which, unlike the
double angle method, does not alter the excitation flip angle and uses an off-resonance pulse to induce a phase shift. The system SNR for our $B_1^+$ mapping sequence data was typically $\sim$300 and at this SNR level the mapping method had higher accuracy and precision than the apparent $B_1^+$ measurement.\textsuperscript{36} Although supplying a $B_1^+$ map is recommended particularly for 2D MESE, further improvements to $B_1^+$ estimation from the decay curve could add constraints on $B_1^+$ solutions, such as comparing results to a $B_1^+$ map template obtained from other studies on the same system. For example, recent work has shown only small $B_1^+$ variations across a large population using a single scanner.\textsuperscript{37} Alternatively, deep learning methods can be used to create an adaptive model that estimates $B_1^+$ maps using multi-echo data.

A limitation of our work is the experimental validation was only for 2D MESE because of the lack of a 3D MESE sequence in our center. However, 3D MESE is an extremely slow approach, if methods such as compressed sensing are not used.\textsuperscript{38} Many groups have recently used a 3D gradient and spin echo (GRASE) technique,\textsuperscript{10,19,20,38,39} although implementations vary between groups because of the complex nature of 3D GRASE. Nevertheless, our simulations show that 3D methods are much less affected by $B_1^+$ misestimations than 2D methods due both to the 2D flip angle effects that remove symmetry around 180° and typically reduced 2D SNR compared to 3D methods.

5 | CONCLUSION

For 2D MESE, because of increased complexity of decay curves and limited SNR, supplying $B_1^+$ improves MWF results in peripheral and central brain regions where flip angles differ substantially from 180°. This proposed approach alleviates further variability that miscalculation of $B_1^+$ may introduce to the NNLS solution.

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