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A diffusion-based method for long- T_2 suppression in steady state sequences: Validation and application for 3D-UTE imaging

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Running Head: Diffusion-based method for long- T_2 suppression in steady state 3D-UTE

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Abstract

Purpose: To introduce a novel method for long- T_2 signal physical suppression in steady-state based on configuration states combination and modulation using diffusion weighting. Its efficiency in yielding a high contrast in short- T_2 structures using an ultrashort echo time acquisition module (Diff-UTE) is compared to the adiabatically prepared Inversion-Recovery-UTE sequence (IR-UTE).

Theory and methods: Using a rectangular-pulse prepared 3D-UTE sequence, the possibility of long- T_2 component signal cancellation through diffusion effects is addressed, and the condition met for sets of sequence parameters. Simultaneously, the short- T_2 component signal is maximized using a Bloch equation-based optimization process. The method is evaluated from simulations, and experiments are conducted on a phantom composed of short and long- T_2 components, as well as on an ex vivo mouse head.

Results: Within equal scan times, the proposed method allowed for an efficient long- T_2 signal suppression, and expectedly yielded a higher signal to noise ratio in short- T_2 structures compared to the IR-UTE technique, although an intrinsic short- T_2 signal loss is expected through the preparation module.

Conclusion: The Diff-UTE method represents an interesting alternative to the IR-UTE technique. Diffusion weighting allowing for a long- T_2 suppression results in a less penalizing method to generate a high and selective contrast in short- T_2 components.

Keywords: ultrashort echo time (UTE); steady state; diffusion; long- T_2 suppression; short- T_2 contrast; preclinical

Abstract word count: 196/200

INTRODUCTION

Ultrashort echo time (UTE) MRI methods are used to acquire and quantify NMR signals from tissues with sub-millisecond transverse relaxation time (T_2). Among them, one can cite cortical bone (1, 2, 3, 4) with strong perspective for CT-like use (5, 6, 7), meniscus (8, 9), tendon (10, 11, 12, 13), lung parenchyma (14, 15, 16), and myelin (17, 18, 19). Since UTE images are mainly proton-density weighted, an efficient method for suppressing water and fat signals (referred hereafter to as long- T_2 components ($T_2 > 10$ ms)) is commonly used with an UTE acquisition scheme to properly exhibit a positive contrast over the solid-like tissues of interest. Several schemes for long- T_2 signal suppression or attenuation have been proposed, such as saturation modules (20, 21), dual echo subtraction (22, 23), or even specific excitation patterns (24) to either null the undesired signal or to selectively excite the component of interest. One of the most frequently used methods to achieve an efficient suppression consists in using an inversion-recovery module in pair with an appropriate inversion time (TI) to physically null the long- T_2 component, followed by an UTE acquisition (22, 25). The IR-UTE sequence has often been adapted into enhanced versions for varied purposes (suppressing fat and water signal (20, 26, 27), filtering short- T_2 signals (28), and acceleration (29)), and has already demonstrated promising results in various applications (3, 19, 27, 30, 31).

Nevertheless, the IR-UTE sequence shows limitations in terms of short- T_2 signal to noise ratio (SNR) generation. Through the use of adiabatic inversion pulses that often saturate the short- T_2 components (21, 32), the available magnetization in the component of interest is governed by its longitudinal recovery during the inversion time delay, itself depending on the T_1 value of the component to be suppressed. Another issue that has to be considered for clinical applications is the elevated Specific Absorption Rate (SAR) induced by the use of adiabatic inversion pulses for long- T_2 signal suppression and short- T_2 signal filtering (28), especially for currently developing ultra-high field scanners.

This study presents a novel method for long- T_2 suppression in a steady-state 3D-UTE sequence through the use of diffusion weighting induced by spoiling gradients, while acquiring

maximized short- T_2 signals (33). The behavior of the method was evaluated from simulations and phantom experiments as a proof of concept on a preclinical scanner. Comparison of the proposed sequence to the IR-UTE sequence was conducted on the same phantom and on an ex vivo mouse head.

THEORY

In the following, the superscripts L and S will indicate the long and short- T_2 component, respectively. Simulated signal relative amplitude will be introduced as $S = |M_{xy}|/M_0$, with M_{xy} transverse magnetization, and M_0 its corresponding magnetization amplitude at thermal equilibrium. To provide a distinction between the two components having respective unknown proton density, it is further quantified in $\%M_0$.

Diff-UTE sequence

The employed pulse sequence (Fig. 1.a) consists in a long ($> T_2^S$) rectangular preparation pulse followed by a short one, whose flip angle is computed to maximize the short- T_2 signal. In steady-state, the approach is somehow similar to the Actual Flip Angle method (34), except that the two consecutive pulses have different flip angles ($\alpha_1 \neq \alpha_2$) and durations, and the readout is performed exclusively after the second pulse. Hence, gradient spoiling, RF spoiling, and delays are optimized to ensure a steady-state of the long- T_2 component to be suppressed, as well as minimizing the impact of potential static gradients (e.g. B_0 inhomogeneities) (35). The sequence aims at removing the long- T_2 signal, while simultaneously maximizing the short- T_2 one, as described in the following sections.

Short- T_2 signal description

Considering the signal of interest arising from the short- T_2 component being fully spoiled before each excitation, its quantity can be tracked using the Bloch equations in steady-state

immediately after the readout pulse ($TE = 0$ ms):

$$S^S = \frac{(1 - E_s) + E_s(1 - E_w)f_{z_1}}{1 - f_{z_1}f_{z_2}E_sE_w}f_{xy}, \quad [1]$$

with $E_s = e^{-TR_1/T_1^S}$, $E_w = e^{-TR_2/T_1^S}$ (TR_1 and TR_2 referring to the internal delays after excitations), $f_{z_i} = e^{-w_i} \left[\cos(\gamma_i) + w_i \text{sinc}(\gamma_i) \right]$, $f_{xy} = e^{-w_2} \alpha_2 \text{sinc}(\gamma_2)$ (with $\gamma_i = \sqrt{\alpha_i^2 - w_i^2}$ and $w_i = \tau_i/2T_2^S$), α_i and τ_i being the respective flip angles and pulse durations. A detailed derivation of the Bloch equations solutions is given in the Appendix. The functions f_{z_i} and f_{xy} account for the signal loss during a hard RF pulse caused by T_2^S relaxation (mapping functions), as described in (36, 37, 38). Including the mapping functions is advantageous and helps quantifying the impact of the durations of the consecutive pulses (22, 39). It therefore allows to adequately model the available S^S signal. Thus, once delays and pulses characteristics are set, the actual short- T_2 signal can be maximized with respect to α_2 as $\hat{\alpha}_2 = \text{argmax}_{\alpha_2}(S^S)$.

Long- T_2 signal description

Once sequence parameters are set, we make use of the steady-state condition in a periodic MR sequence to suppress the water signal. The long- T_2 signal can be modeled by any simulation framework taking diffusion into account (40, 41). Thus, using the expression for configuration states in (42), the signal to be suppressed can be written:

$$F_0^+ = \cos^2(\alpha_2/2)F_0^- + e^{2i\Phi} \sin^2(\alpha_2/2)^2 F_0^{-*} - ie^{i\Phi} \sin(\alpha_2)Z_0^-, \quad [2]$$

with F_0^- and Z_0^- being functions of α_1 , α_2 , RF-phase Φ , TR_1 , TR_2 , T_1^L , T_2^L , gradient spoiling areas $G\delta$ and $G\delta'$ in respective internal segments TR_1 and TR_2 , and tissue diffusion characteristics. In this case, having $|F_0^+| = 0$ would imply a complete long- T_2 suppression. Since no trivial analytical expression exists for the F_0^- and Z_0^- states in steady-state, we numerically explored the tissues and sequence parameter space in order to assess whether

the diffusion weighting induced by the spoiling gradients would combine the F_0^- and Z_0^- states in order to satisfy $|F_0^+| = 0$. This condition can be met for sets of parameters and RF-phase increment $\Phi_0 = k \times 360/(n + 1)$ ($k \in \mathbb{Z}$, $n = TR_2/TR_1 \geq 2$), offering a signal falling to 0 (referred hereafter to as “signal minimum”).

In the following, the apparent diffusion coefficient D will be assimilated to that of the single spoiling direction used in experiments (i.e. z -direction). Hence, and for better readability, diffusion weighting is quantified in terms of gradient spoiling moment $G\delta$, equal to the gradient area in the first internal delay TR_1 . To maintain a steady-state condition, the spoiling gradient areas ratio $G\delta'/G\delta$ is set to be equal to n (35).

Finally, given a specific isotropic geometry and receiving bandwidth, the minimum spoiling moment to provide a 2π spin dephasing across a voxel in TR_1 amounts to:

$$(G\delta)_{min} = G_{read}\tau_{read}. \quad [3]$$

The resulting minimum spoiling moment in TR_2 is equal to $n \times (G\delta)_{min}$, yielding a zero-order b-value difference between the readout (considering an isotropic diffusion for simplification purpose since the readout gradients vary within each repetition) and the spoiling gradients in TR_2 of about n^3 (43). Hence, the diffusion weighting contributions from the readout gradients will further be neglected.

METHODS

Long and short- T_2 magnetizations behavior hypotheses

Throughout the paper, the following hypotheses (summarized in Table 1) regarding the long and short- T_2 components are made:

- the short- T_2 component being considered to have a fully decayed transverse magnetization prior to the excitations, any contribution of diffusion weighting by spoiling

gradients is assumed negligible as it does not affect the magnetization. Hence, its relative amplitude can be simulated using Eq. [1], and exclusively depends on τ_1 , τ_2 , flip angles α_1 and α_2 , T_1^S , T_2^S and sequence delays. Alternatively, the adiabatic inversion pulse used in IR-UTE is supposed to saturate the short- T_2 component given its assumed sub-millisecond T_2 value in simulations and experiments (29, 32).

- the long- T_2 component is affected by diffusion weighting through the spoiling gradients $G\delta$ and $G\delta'$, flip angles α_1 and α_2 , apparent diffusion coefficient D , T_1^L , T_2^L and sequence delays. Similarly, relaxation during excitations is assumed negligible, and adiabatic inversion is supposed to fully invert the component's magnetization.

Optimization of the Diff-UTE sequence parameters

Once long and short- T_2 components parameters and sequence delays have been set, generating the highest contrast in the short- T_2 component consists in stretching τ_1 to take advantage of the relaxation occurring during excitation, contracting τ_2 to ensure a maximum excitation, and adapting α_1 , α_2 and $G\delta$ to maximize the short- T_2 components signal while nulling the long- T_2 one through the states combination process.

The following is an example of algorithm for the sequence parameters choice: (i) provide expected tissues/materials properties T_1^L/T_2^L , D and T_1^S/T_2^S ; (ii) set system parameters RF-phase Φ , TR_2/TR_1 , τ_1 and τ_2 respecting hardware limitations; (iii) set preparation pulse flip angle α_1 ; (iv) optimize α_2 to maximize the short- T_2 signal; (v) search $G\delta$ numerically to minimize the long- T_2 signal through the readout excitation pulse; (vi) if $G\delta$ is non-existent or too high for the user's hardware capacities, loop to step (iii) and modify α_1 accordingly.

Even though this method allows to guarantee a theoretical short- T_2 signal maximization, converging to a suitable solution $G\delta$ may necessitate further exploration of α_1 and α_2 . Figures S1 to S6 in Supporting Information provide additional simulations to get a better understanding of the long- T_2 signal behavior regarding the numerous parameters.

Particular considerations

The sequence repetition time in the experiments are equal to (Fig. 1):

$$TR = \tau_1 + TR_1 + \tau_2 + TR_2 \quad \text{in Diff-UTE} \quad [4]$$

$$TR = \tau_{inv} + TI + \tau_{IR} + RD \quad \text{in IR-UTE} \quad [5]$$

with τ_{inv} and τ_{IR} preparation and readout pulse durations in IR-UTE, respectively. Internal delays after preparation and readout pulses are respectively designated as TI and RD in the same sequence. In addition, when both methods are compared to each other, the repetition time is kept constant in both sequences so that the acquisition times are identical, and hence global signals comparable to each other.

Using the notation in Eq. [5] and Bloch equations, it can be shown that signal suppression in IR-UTE is performed by setting the TI delay to:

$$TI = -T_1^L \ln \left((1 + e^{-(TR - \tau_{inv} - \tau_{IR})/T_1^L}) / 2 \right), \quad [6]$$

with T_1^L longitudinal relaxation time of the fully inverted long- T_2 component. Additionally, due to the saturated condition of the short- T_2 magnetization after inversion (inversion efficiency $Q = 0$), the relative amplitude can be expressed as (18) ($TE = 0$ ms):

$$S_{\text{IR-UTE}}^S = (1 - e^{-TI/T_1^S}) f_{xy}^{IR}, \quad [7]$$

with f_{xy}^{IR} the corresponding transverse mapping function of the readout pulse in IR-UTE.

Alternatively, an unprepared UTE sequence ($\alpha_1 = 0^\circ$ in Diff-UTE) with an echo-subtraction technique to suppress the long- T_2 signal is considered (22) and used to quantify the expected short- T_2 signal loss through the preparation module in Diff-UTE. Using the notations of the Diff-UTE sequence, the resulting resting delay between two consecutive excitations is equal to $RD = \tau_1 + TR_1 + TR_2$. The short- T_2 signal in this sequence is therefore described by

($TE = 0$ ms):

$$S_{\text{UTE}}^S = \frac{1 - E_r}{1 - E_r f_z} f_{xy}, \quad [8]$$

with $E_r = e^{-RD/T_1^S}$, and f_z and f_{xy} the corresponding mapping functions of the unique excitation pulse. From Equation [8], an optimized excitation flip angle can be evaluated similarly to the Diff-UTE short- T_2 signal optimization process, as described in (39). Finally, the ratio of both optimized signal, is expressed as:

$$R = \frac{S_{\text{Diff-UTE}}^S}{S_{\text{UTE}}^S} \sqrt{2}, \quad [9]$$

where the $\sqrt{2}$ factor takes account of the SNR loss through the echo subtraction process in the unprepared UTE sequence to yield a theoretical long- T_2 signal suppression (21, 32).

Numerical simulations

If not otherwise stated, all numerical simulations were done using the following nominal relaxing and diffusion parameters: long- T_2 component: $D = 1.00 \mu\text{m}^2/\text{ms}$, $T_1^L/T_2^L = 1000/100$ ms; short- T_2 component: $T_1^S/T_2^S = 300/0.315$ ms. In Diff-UTE, invariable parameters are intermediary delays $TR_1/TR_2 = 5/25$ ms, and readout pulse duration $\tau_2 = 0.07$ ms. The short- T_2 parameters are that of the Lego brick sample used in experiments ($T_1^S/T_2^S = 300/0.315$ ms, assuming its T_2 value to be close to T_2^* (1, 18, 36)). Simulations and analyses of the long- T_2 signal were performed using the Extended Phase Graph formalism (42, 41, 44), with adapted code available at http://epg.matthias-weigel.net/ge_ssfepg.html.

Long- T_2 signal simulations using Diff-UTE were performed. Its signal variability along gradient spoiling moments ranging from 0.0 to 500.0 mT/m.ms was evaluated for different preparation flip angles α_1 ranging from 60° to 90° , $\tau_1 = 1$ ms, and an optimized α_2 for each value. Similarly, the short- T_2 signal is evaluated for optimized parameters given the same α_1 range, and τ_1 values from 0.5 to 3 ms.

In order to provide insights about the robustness of the suppression in case of inaccuracies

of the estimated relaxing and diffusion parameters, signal minima occurrences are explored through the long- T_2 relaxing and diffusion parameters. One out of three parameters is made varying about $\pm 50\%$ of its nominal values along a constant spoiling gradient moment range from 0.0 to 300.0 mT/m.ms for $\alpha_1 = 80.0^\circ$ and an optimized $\alpha_2 = 57.0^\circ$ maximizing a $T_1^S/T_2^S = 300/0.315$ ms species.

Specific tissues long- T_2 signal behavior were assessed in Diff-UTE. Relaxation and diffusion parameters were chosen from the literature at 3 T (45, 35, 46, 47): $T_1/T_2 = 1412/50$ ms and $D = 0.7 \mu\text{m}^2/\text{ms}$ for skeletal muscle, $T_1/T_2 = 4000/2000$ ms and $D = 2.2 \mu\text{m}^2/\text{ms}$ for cerebrospinal fluid, $T_1/T_2 = 1820/99$ ms and $D = 0.8 \mu\text{m}^2/\text{ms}$ for grey matter, and $T_1/T_2 = 1084/69$ ms and $D = 0.8 \mu\text{m}^2/\text{ms}$ for white matter. Preparation and excitation flip angles are $\alpha_1/\alpha_2 = 80/57^\circ$.

The short- T_2 signal ratio between Diff-UTE and IR-UTE is generated for the most penalizing preparation flip angle $\alpha_1 = 90^\circ$ and optimized α_2 , and for T_1^S and T_2^S respectively ranging from 100 to 1000 ms and 0.1 to 1 ms. Alternatively, the same quantity was generated for arbitrary α_1 and α_2 respectively ranging from 60 to 90° and 1 to 90°, and for $T_1^S/T_2^S = 300/0.315$ ms. For both simulations, the IR-UTE sequence parameters are optimized to yield a long- T_2 signal cancellation having a T_1^L of 1000 ms (i.e. $TI = 11.5$ ms), and with $\tau_1/\tau_{inv}/\tau_{IR} = 1/8/0.07$ ms.

Finally, in order to assess the maximal signal loss induced by the preparation in Diff-UTE, the R ratio is computed within respective optimized conditions of $S_{\text{Diff-UTE}}^S$ and S_{UTE}^S , and with identical excitation pulse duration and repetition time. In Diff-UTE, τ_1 is ranging from 0.5 to 5 ms and α_1 from 60 to 90°.

Experimental details

Experiments were conducted on a 7T BioSpec 70/30 USR small animal MRI system (Bruker BioSpin MRI GmbH, Ettlingen, Germany), operated with ParaVision 6.0.1. Gradient system provided a maximum amplitude of 442 mT/m, and a maximum slew rate of 3660 T/m/s.

Scans were performed using a 86-mm diameter transmitter, and a mouse surface coil for reception. The native UTE-3D Bruker sequence was modified and declined into the proposed sequence (Fig. 1.a), as well as in IR-UTE (Fig. 1.b). A high-order B_0 shimming was systematically estimated prior to acquisition series. To compensate for eddy currents and gradients non-idealities (48), spokes trajectories were measured using the constructor’s routine (49). Images were then reconstructed using the built-in software reconstruction pipeline.

Since the imaged phantom is considered as an homogeneous item, voxels size was chosen to be large compared to the ex vivo sample experiments in order to avoid a prohibitive total acquisition time.

Phantom

A phantom composed of an ABS plastic Lego brick immersed in a doped distilled water with Ni^{2+} , 2Cl^- ($C_{\text{Ni}^{2+}} = 1 \text{ mM}$; prior scans using gold-standard sequences allowed to estimate the following parameters at bore temperature ($\approx 20^\circ\text{C}$): $D = 1.81 \mu\text{m}^2/\text{ms}$ using a pulsed field gradient spin-echo sequence (PGSE), $T_1^L = 590 \text{ ms}$ using an inversion-recovery spin-echo sequence (IR-SE), and $T_2^L = 295 \text{ ms}$ using a multi spin-echo sequence (MSE)). Relevant sequence parameters in phantom experiments were: RF phase increment $\Phi_0 = 0^\circ$, receiver bandwidth = 150 kHz, matrix size = $96 \times 96 \times 96$, voxel size = 0.26 mm isotropic, number of radial lines = 28733, dummy scans = 200. Again, in Diff-UTE, invariable parameters are intermediary delays $TR_1/TR_2 = 5/25 \text{ ms}$, and readout pulse duration $\tau_2 = 0.07 \text{ ms}$.

A first estimation of the T_2^{S*} value of the Lego brick was made using a single-pulse sequence: TR = 4000 ms, $50 \mu\text{s}/90^\circ$ rectangular pulse, receiver bandwidth = 50 kHz, 64 averages.

The possibility of long- T_2 signal cancellation in Diff-UTE is assessed for different optimized sets of flip angles $\{\alpha_1/\alpha_2\} = \{90.0^\circ/62.1^\circ, 80.0^\circ/57.0^\circ, 70.0^\circ/51.8^\circ, 60.0^\circ/46.7^\circ\}$. τ_1 and TE was set to 1 and 0.02 ms, respectively, amounting an acquisition time per scan to 14 min and 52 s. To explore the diffusion effects, 24 gradient spoiling moment values linearly

spaced from 120.2 to 488.2 mT/m.ms were used, the lowest value corresponding to a gradient spoiling moment sufficiently strong to yield an artifact-free volume.

A comparison of the short- T_2 SNR estimated in Diff-UTE and IR-UTE was conducted within long- T_2 suppression conditions. Short- T_2 signal was acquired using the same readout pulse duration $\tau_2 = \tau_{IR} = 0.07$ ms and same $TE = 0.02$ ms. For an optimal $G\delta$ value in Diff-UTE, a scan was acquired using the previously proposed protocol. An 8-ms effective 1.75 kHz single-band inversion hyperbolic secant adiabatic pulse (50) was employed in IR-UTE, whose duration and bandwidth are set to be consistent to that employed in the literature which used 8.6 ms and 1.5 kHz pulses (3, 29). TR was kept identical in both sequences in order to equal acquisition times for each increment, while respective sequences delays obey Eq. [4] and [5]. In addition, readout flip angle α_{IR} in IR-UTE was set to 90° to ensure a maximum SNR of the short- T_2 component, and a sufficiently strong and long gradient spoiling was used to provide a dephasing moment superior to 2π after inversion and readout. For each TR values amounting to $\{TR\} = \{31.07/31.57/32.07/32.57/33.07\}$ ms following an increasing $\{\tau_1\} = \{1.0/1.5/2.0/2.5/3.0\}$ ms, theoretical α_2 optimal values given a constant $\alpha_1 = 80.0^\circ$ were used: $\{\alpha_2\} = \{57.0^\circ/51.3^\circ/47.4^\circ/44.6^\circ/42.5^\circ\}$, yielding optimal $\{G\delta\} = \{159.1/203.3/229.8/238.7/247.5\}$ mT/m.ms in Diff-UTE. In IR-UTE, given the extending TR, appropriate inversion delays were computed: $\{TI\} = \{11.5/11.7/11.9/12.1/12.3\}$ ms.

Ex vivo sample

A C57BL/6 adult mouse was perfused via intra-cardiac delivery of PBS followed by tissue fixation using 4% paraformaldehyde (51). All the procedures were done under deep anesthesia and in accordance to the local ethical committee rules. The head was collected and soaked into a proton-free solution (PFPE, Galden, Solvay) and scanned using both UTE sequences along with a 2D Fast Low Angle SHot (FLASH; $TR/TE = 50/5$ ms, slice thickness = 0.5 mm, in-plane voxels size = $78 \times 78 \mu\text{m}^2$, 32 averages, acquisition time/scan = 6 min 49 s). Prior scans (IR-SE, MSE and PGSE) allowed to estimate relaxing constants and diffusion

characteristic in the gray matter, yielding a T_1 of 923 ± 8.1 ms, a T_2 of 70 ± 2.5 ms, and a diffusion coefficient along the spoiling direction of $0.328 \pm 0.011 \mu\text{m}^2/\text{ms}$. Approximated T_1 and T_2 values of the cortical bone at room temperature found in (52) were used for Diff-UTE parameters optimization ($T_1 = 120$ ms, $T_2 = 0.4$ ms). Common parameters were $TR/TE = 33.07/0.01$ ms, RF phase increment $\Phi_0 = 0^\circ$, voxel size = 0.104 mm isotropic, matrix size = $192 \times 192 \times 192$, number of radial lines = 57527 (undersampling factor = 2) and receiver bandwidth = 200 kHz, acquisition time/scan = 31 min 42 s. Specific parameters were $TR_1/TR_2 = 5/25$ ms, $\tau_1/\tau_2 = 3/0.07$ ms, $\alpha_1/\alpha_2 = 90.0/40.0^\circ$ and $G\delta = 88.4$ mT/m.ms in Diff-UTE; 8-ms/1.75 kHz hyperbolic secant adiabatic inversion pulse, $\tau_{IR} = 0.07$ ms, $\alpha_{IR} = 90.0^\circ$ and $TI = 12.4$ ms in IR-UTE.

RESULTS

Simulations

Signal minima occurrences are depicted in blue bands on figures relating simulation results. It corresponds to an arbitrary threshold considered when the evaluated long- T_2 transverse magnetization has reached 0.05% of its value at thermal equilibrium.

As shown in Figure 2.a, signal minima are reachable given an initial tip angle α_1 threshold of 76° given the proposed optimization pipeline and used set of parameters. For intermediary α_1 values between 79° and 87° , two $G\delta$ -ranges for suppression can be theoretically yielded, and a single range is finally obtained for α_1 between 88° and 90° . Figure 2.b illustrates the relative short- T_2 signal amplitude S^S as a function of α_1 and τ_1 . As τ_1 increases, the relaxation-excitation effect becomes all the more important, leading to a higher short- T_2 theoretical signal. Additionally, the black dashed line indicates the domain where long- T_2 signal suppression can be achieved, and illustrates the dependency of α_2 to τ_1 through the optimization process.

Figure 3 illustrates the signal minima occurrences sensitivity about T_1^L , T_2^L and D . The

suppression method being based on configuration states' population modulation given the component relaxing and diffusion characteristics, the tolerance to suppression is surprisingly robust to deviations of such parameters for variations about $\pm 25\%$. In T_1 and T_2 figures, the suppression bands join at extreme negative deviations, while the D parameter seems rather robust in spite of strong deviations.

Figure 4 shows the long- T_2 signal behavior of various biological tissues. Theoretical long- T_2 suppressions can rigorously be generated for every tissue, except for the skeletal muscle, most likely due to the relatively low T_2 and apparent diffusion coefficient D . Nonetheless, it can be considered suppressed under the threshold condition $S^L < 0.05\%M_0$ in a $G\delta$ range between 97 and 172 mT/m.ms.

Figure 5.a shows the ratio of short- T_2 signals generated in Diff-UTE and IR-UTE. Given the simulation parameters, the ratio reaches values below 1.0 in extreme parameters $T_1^S < 262$ ms and $T_2^S > 0.91$ ms, the lowest ratio being equal to 0.96 for $T_1^S/T_2^S = 100/1$ ms. Figure 5.b shows the same ratio as a function of arbitrary α_1 and α_2 for $T_1^S/T_2^S = 300/0.315$ ms. This indicates a much higher signal generation in Diff-UTE for low flip angles values, but careful attention shall be given in that a long- T_2 suppression condition is not systematically reachable in Diff-UTE for such regimes.

Figure 6 shows the ratio R as a function of τ_1 and α_1 . Given a constant α_1 , R increases as τ_1 does due to the increasing short- T_2 relaxation occurring during the excitation. Even though this effect allows for more short- T_2 signal generation in Diff-UTE as τ_1 increases, the signal generated by the unprepared UTE sequence is intrinsically higher since an additional T_1 relaxation effect occurs. The highest ratio is generated for $\alpha_1 = 60^\circ$ and $\tau_1 = 5$ ms ($R = 0.996$). Within the conditions in experiments (i.e. $\alpha_1 = 90^\circ$, $\tau_1 = 1$ ms), the estimated loss amounts to 58%.

Experiments

The acquired signal in the single pulse sequence showed a spectral line's frequency width half magnitude resulting in a T_2^{S*} of about 315 μ s. In IR-UTE, the appropriate TI (from Equation [6]) nulling a T_1^L of 590 ms ($TI = 11.48$ ms) is close to that of a T_1^L of 1000 ms component ($TI = 11.53$ ms). Hence, the conditions of simulations from Figure 5.a being similar, the ratio of the short- T_2 signals generated in Diff-UTE and IR-UTE is systematically superior to 2.5 with the previously estimated T_2^S for T_1^S ranging from 100 to 1000 ms. As a result and given the operating field in experiments (7 T), T_1^S was further extrapolated from reported value at 105.6 MHz (53) ($T_1 \approx 150$ ms) to 300 ms for simulations and parameters optimization purposes.

Figure 7 shows doped-water and Lego brick signal intensities against spoiling gradient moment for four preparation flip angles α_1 , as well as relevant coronal views from the phantom. Maximal contrast between long- and short- T_2 components was obtained for intermediary $G\delta$ amplitudes for suppression-yielding α_1 values of 80° and 90°. Signal suppression, if any, is obviously capped to the noise level, as depicted on the graphics. Theoretical and experimental long-relaxing signals tendencies are in good agreement with each other, suggesting an appropriate description of the long- T_2 signal. While the long- T_2 signal is made varying with $G\delta$, no noticeable impact over the short- T_2 component signal at a given $\{\alpha_1; \alpha_2\}$ pair is observed, suggesting that the proposed suppression scheme does not affect the component of interest. However, as expected, the higher the preparation flip angle α_1 , the lower the short- T_2 signal amplitude.

In a long- T_2 suppression condition, the effective SNR in the short- T_2 component is systematically higher in Diff-UTE than in IR-UTE, with respective ratios of 1.49, 1.70, 1.95, 2.03 and 2.31 for TR of 31.07, 31.57, 32.07, 32.57 and 33.07 ms. The ratio evolution along the increasing TR shows that the suppression scheme in Diff-UTE is less penalizing than in IR-UTE regarding the short- T_2 component signal. Figure 8 illustrates the results with views of the phantom acquired at TR of 31.07 and 33.07 ms in both sequences.

Figure 9 shows the fixed mouse head coronal and sagittal central views in FLASH, Diff-UTE and IR-UTE. Soft tissues are very well perceptible in the FLASH sequence, and no signal is visible in the head skull. On the contrary, a fairly good contrast on the cortical bone of the head skull is generated in both UTE sequences. SNR were calculated using the drawn ROI in the skull, and amounted respectively to 14.0 and 5.4 in Diff-UTE and IR-UTE, supporting simulations and previous experiments results about the short- T_2 signal generation efficiency using the proposed method.

DISCUSSION

A novel method for suppressing a long- T_2 component has been proposed. Similarly to the inversion-recovery approach, the method has proven to be efficient in suppressing contaminating signal, therefore yielding a high contrast in short- T_2 structures in an UTE acquisition sequence. Additionally, a compelling SNR in plastic polymer and cortical bone was generated through the proposed optimization process, making the approach all the more promising for further applications in imaging short- T_2 structures.

The higher SNR generated in pair with a 3D modality in the proposed method may be beneficial for various purposes. For example, sequence acceleration can be made possible through several already-established processes. Due to the expected higher short- T_2 transverse magnetization in Diff-UTE compared to the IR-UTE sequence, one can take advantage of the available short- T_2 magnetization to proceed to undersampling, or even implement a multi-spoke acquisition pattern within a single TR (29, 54), however at the cost of a less efficient suppression, and although limited by the required short TR to ensure a steady-state. In a clinical application, these features may consequently reduce scan time for a whole 3D-coverage. On another hand, small voxel sizes are also responsible for a loss of SNR, as is the case in high-resolution imaging or in preclinical scanner applications, even though ultra high fields used in the latter aim to compensate for it.

In this study, scan times may seem quite long for the ex vivo sample (≈ 31 min). This was due in this case i) to the relatively small voxels size yielding a rather low signal intensity and inducing SNR loss in case of a further increasing undersampling factor, and ii) to generate a distinguishable contrast in IR-UTE to be compared with the proposed method. More sensitive devices, as well as more flexible acquisition schemes (2, 55) may help taking advantage of the required short TR to reduce the acquisition scan times.

As proposed in the literature (22, 56), a second echo may be acquired after reading and refocusing the first FID. This may come in handy if ones want to suppress fat signal through a magnitude subtraction process, for example, by setting an appropriate echo time in order to provide an in-phase signal refocusing. Additional fat suppression may also be performed by appropriately including an optimized off-resonance pulse centered at 3.5 ppm in the pulse sequence.

In ex vivo experiments, a strong global suppression and attenuation of the contaminating long- T_2 signals (white and grey matter) has been noticed. This is inherent to the short TR used in the Diff-UTE protocol, as is also the case in IR-UTE. For instance, the needed parameter — here TI — does not vary much for suppressing a wide range of T_1 , somehow yielding a large suppression of T_1 species, or at least a significant signal attenuation. When coupled with an efficient scheme for short- T_2 signal maximization, a substantially higher contrast to noise ratio in regions of interest is generated compared to the IR-UTE. These specific aspects may be of a great advantage in in vivo experiments as residual water signals are suppressed through an echo-subtraction technique (5, 18, 32), therefore diminishing the relative SNR in studied structures.

Another advantage of the radial 3D acquisition modality is the non-selective excitation: commonly used reshaped pulses (57) in 2D-UTE methods are sensitive to intrinsic sequence imperfections such as eddy currents inducing slice-select and readout gradients distortions (58, 59), timing errors between slice-selective gradients and RF amplifier (60, 61), and off-resonance effects that may cause slice distortions (62). These are also penalizing due

to T_2 decay during the relatively long selective excitation (22).

No adiabatic pulse is used in Diff-UTE, but a global suppression of long relaxing signals has nonetheless been reached. This represents a great advantage in terms of RF power deposition, as well as compensating for clinical scanner limitations as the available B_1 peak is often low on such systems. For example, the pulses used in the ex vivo experiment yielded a relative SAR for the first order HS about 12.7 times higher in IR-UTE than the preparation rectangular pulse in Diff-UTE. This score was generated by using a $B_{1,max}$ of 17 μT for the HS pulse, corresponding to the minimum RF amplitude to yield an efficient inversion ($Q < -0.99$ (63)). The latter was estimated by numerically solving the Bloch equations, assuming that no relaxation occurs during the inversion. The relative SAR expressions are given in Appendix. As a result, the method is well suited for ultra-high field scanners' applications where protocols can be greatly limited by the SAR.

So far, α_2 was set using the proposed optimization process where its estimation relies on the assumption of priors about T_1 and T_2 values of a single short relaxing component. However, a wide short- T_2 distribution is often found in solid-like structures, essentially due to their complexity. For example, the transverse magnetization decay of the Lego brick indicates the presence of at least two components, as shown in Figure S7. This multicomponent behavior can also be regarded as a more realistic pattern of what can be found in biological tissues (4, 64, 65, 66). Hence, assuming a single-relaxing component in such systems may result in a short- T_2 selectivity pattern since its signal will be maximized with no particular regards to other short relaxing components. As such, SNR quantification in solid-like structures may vary with the respective proton density and relaxation time constants of the various excited pools, given sets of parameters. A more complex optimization scheme for α_2 optimization can be established under the condition of acknowledging the respective relaxing parameters, as well as their relative proton density fractions. An expected propagation of uncertainties regarding the experimental signal intensities may arise from such increasingly complexity. Nonetheless, a substantially higher SNR was found in our experiments when

comparing both UTE sequences, supporting our simulations' trends.

Filtering short- T_2 and slightly short- T_2 components has also been reported in (28) through adiabatic pulses combination by taking advantage of a partial inversion effect instead of a saturation of species having T_2 above 2 ms. While this filter is constituted by adiabatic inversion pulses in IR-UTE-like sequences, this can also be performed through steady-state and flip angles combinations in Diff-UTE. In the same manner as in IR-UTE and its adapted versions, a filtering effect of the short- T_2 components can be made through the long- T_2 suppression scheme, as well as the chosen short-relaxing compartment parameters in the maximization process, hence maximizing one component over the other. It has been shown in Figure 9 that a higher SNR can be generated with the proposed sequence compared to the IR-UTE, but no attention was given about the multicomponent behavior of the cortical bone. Further investigations may allow to discriminate appropriately the various short- T_2 pools present in such structure.

The long- T_2 suppression method was proposed in the present paper for generating contrast in sub-millisecond relaxing transverse structures. Given the advantages discussed above, an adaptation of such technique offering new kinds of selectivities (relaxation and diffusion) may represent an interesting and rapid approach for novel contrasts generation in soft tissues. Further investigations will be led accordingly.

As a prepared sequence, a loss of magnetization of the short- T_2 component is to be expected compared to an unprepared sequence with equal TR . An echo subtraction technique may be included in the latter for long- T_2 suppression purpose, at the cost of an inherent reduced SNR by a $\sqrt{2}$ factor (21, 32). Additionally, Equation [9] remains exclusively valid under the ideal condition of a fully relaxed short- T_2 component by the second echo. If not, as it might be the case for the longest T_2 component in cortical bone ($T_2^* \approx 1.1$ ms at 3 T (1)) for TE about 2 ms for example, this will result in an increased short- T_2 signal penalization in the unprepared UTE sequence. In the same manner, the method proposed by Johnson et al. (5) takes advantage of the respective relaxing signal differences by performing

a magnitude subtraction of an image acquired with a short pulse and a short TE , and an image acquired with a long pulse and a long TE , using the same flip angles. In spite of a doubled acquisition time, such process may yield a slightly higher short- T_2 SNR in the resulting unprepared and subtracted image since the residual short- T_2 components in the late TE are less excited within the long pulse. Other issues may occur, such as additional tissue-dependent long- T_2 relaxation between echoes, diffusion weighting through readout and refocusing gradients prior to the acquisition of the second echo (67, 68), or even susceptibility effects (20). These irreversible effects are therefore responsible for a physical impossibility of long- T_2 suppression, all the more important when dealing with small voxels sizes and increasing operating static field.

CONCLUSION

A novel long- T_2 suppression method which employs diffusion induced weighting in a steady-state 3D-UTE sequence has been presented. Simultaneously, the sequence provides more degrees of freedom to maximize the short- T_2 signal quantity compared to the IR-UTE sequence. A good contrast was obtained with each sequence, and a compelling higher SNR was estimated in a mouse head skull in Diff-UTE compared to IR-UTE.

Supporting Information

Additional Supporting Information may be found in the online version of this article.

Fig. S1. S^L as a function of α_1 (in degrees) and $G\delta$ (in mT/m.ms), for $T_2^L = 25/50/100/1000$ ms (columns), and $\alpha_2 = 15/30/45/60/75/90^\circ$ (rows). Other simulation parameters: $T_1^L = 1000$ ms, $D = 0.3 \mu\text{m}^2/\text{ms}$ and $TR_1/TR_2 = 5/25$ ms. Signal minima occurrences ($S^L < 0.05\%M_0$) are depicted in the blue bands.

Fig. S2. S^L as a function of α_1 (in degrees) and $G\delta$ (in mT/m.ms), for $T_2^L = 25/50/100/1000$ ms (columns), and $\alpha_2 = 15/30/45/60/75/90^\circ$ (rows). Other simulation parameters: $T_1^L =$

1000 ms, $D = 0.8 \mu\text{m}^2/\text{ms}$ and $TR_1/TR_2 = 5/25$ ms. Signal minima occurrences ($S^L < 0.05\%M_0$) are depicted in the blue bands.

Fig. S3. S^L as a function of α_1 (in degrees) and $G\delta$ (in mT/m.ms), for $T_2^L = 25/50/100/1000$ ms (columns), and $\alpha_2 = 15/30/45/60/75/90^\circ$ (rows). Other simulation parameters: $T_1^L = 1000$ ms, $D = 2.0 \mu\text{m}^2/\text{ms}$ and $TR_1/TR_2 = 5/25$ ms. Signal minima occurrences ($S^L < 0.05\%M_0$) are depicted in the blue bands.

Fig. S4. S^L as a function of α_1 (in degrees) and $G\delta$ (in mT/m.ms), for $T_2^L = 25/50/100/1000$ ms (columns), and $\alpha_2 = 15/30/45/60/75/90^\circ$ (rows). Other simulation parameters: $T_1^L = 1400$ ms, $D = 0.3 \mu\text{m}^2/\text{ms}$ and $TR_1/TR_2 = 5/25$ ms. Signal minima occurrences ($S^L < 0.05\%M_0$) are depicted in the blue bands.

Fig. S5. S^L as a function of α_1 (in degrees) and $G\delta$ (in mT/m.ms), for $T_2^L = 25/50/100/1000$ ms (columns), and $\alpha_2 = 15/30/45/60/75/90^\circ$ (rows). Other simulation parameters: $T_1^L = 1400$ ms, $D = 0.8 \mu\text{m}^2/\text{ms}$ and $TR_1/TR_2 = 5/25$ ms. Signal minima occurrences ($S^L < 0.05\%M_0$) are depicted in the blue bands.

Fig. S6. S^L as a function of α_1 (in degrees) and $G\delta$ (in mT/m.ms), for $T_2^L = 25/50/100/1000$ ms (columns), and $\alpha_2 = 15/30/45/60/75/90^\circ$ (rows). Other simulation parameters: $T_1^L = 1400$ ms, $D = 2.0 \mu\text{m}^2/\text{ms}$ and $TR_1/TR_2 = 5/25$ ms. Signal minima occurrences ($S^L < 0.05\%M_0$) are depicted in the blue bands.

Fig. S7. Fittings of the Lego brick experimental signal (circles). Bi-component fitting is depicted in dashed line, mono-component in dotted line, and noise level in crosses. Diff-UTE parameters were: $TR = 31.07$ ms ($TR_1/TR_2 = 5/25$ ms, $\tau_1/\tau_2 = 1/0.07$ ms), $\alpha_1/\alpha_2 = 80.0/57.0^\circ$, $G\delta = 159.12$ mT/m.ms, and $TE = 0.02, 0.03, 0.05, 0.10, 0.15, 0.25, 0.40, 1.10, 1.80$ ms. Bi-component estimation yielded $T_2^{*S,1} = 0.18 \pm 0.05$ ms ($F^{S,1} = 57.6 \pm 9.5\%$), and $T_2^{*S,2} = 1.63 \pm 0.52$ ms ($F^{S,2} = 42.4 \pm 10.4\%$) ($R_{adj}^2 = 0.99$), and mono-component $T_2^* = 0.52 \pm 0.09$ ms ($R_{adj}^2 = 0.94$).

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APPENDIX

Short- T_2 signal derivation

The signal of interest S^S is acquired after the excitation pulse $\{\alpha_2/\tau_2\}$. Assuming a complete spoiling before each excitation (i.e. $T_2 \ll \{TR_1; TR_2\}$), one can track the short- T_2 longitudinal magnetization from one repetition to another in a steady-state condition using the Bloch equations :

$$\begin{cases} M_z^S(\tau_2) &= M_z^S(TR_1) \times f_{z_2} \\ M_z^S(TR_2) &= M_0 - (M_0 - M_z^S(\tau_2)) E_w \\ M_z^S(\tau_1) &= M_z^S(TR_2) \times f_{z_1} \\ M_z^S(TR_1) &= M_0 - (M_0 - M_z^S(\tau_1)) E_s \end{cases} \quad [10]$$

noting $M_z^S(t_i)$ the longitudinal magnetization after the delay t_i , and with $E_s = e^{-TR_1/T_1^S}$, $E_w = e^{-TR_2/T_1^S}$ (TR_1 and TR_2 referring to the internal delays after excitations), $f_{z_i} = e^{-w_i} \left[\cos(\gamma_i) + w_i \text{sinc}(\gamma_i) \right]$ (with $\gamma_i = \sqrt{\alpha_i^2 - w_i^2}$ and $w_i = \tau_i/2T_2^S$), α_i and τ_i being the respective flip angles and pulse durations. It therefore yields :

$$M_z^S(TR_1) = M_0 \frac{(1 - E_s) + E_s(1 - E_w)f_{z_1}}{1 - f_{z_1}f_{z_2}E_sE_w}, \quad [11]$$

providing the normalized transverse magnetization after the excitation pulse in equation [1].

SAR expressions

With no particular regards about the duty cycle, the relative SAR Γ of the pulses used in experiments can be expressed as (69, 70) :

$$\Gamma_{HS} \propto \frac{B_{1,max}^2 \tau_{IR}}{\beta} \quad \text{for a first order HS pulse,} \quad [12]$$

$$\Gamma_{BP} \propto B_{1,max}^2 \tau_1 \quad \text{for a rectangular pulse,} \quad [13]$$

with $B_{1,max}$ the respective pulse maximum amplitude, and $\beta \approx 5.3$ truncation factor of the HS pulse.

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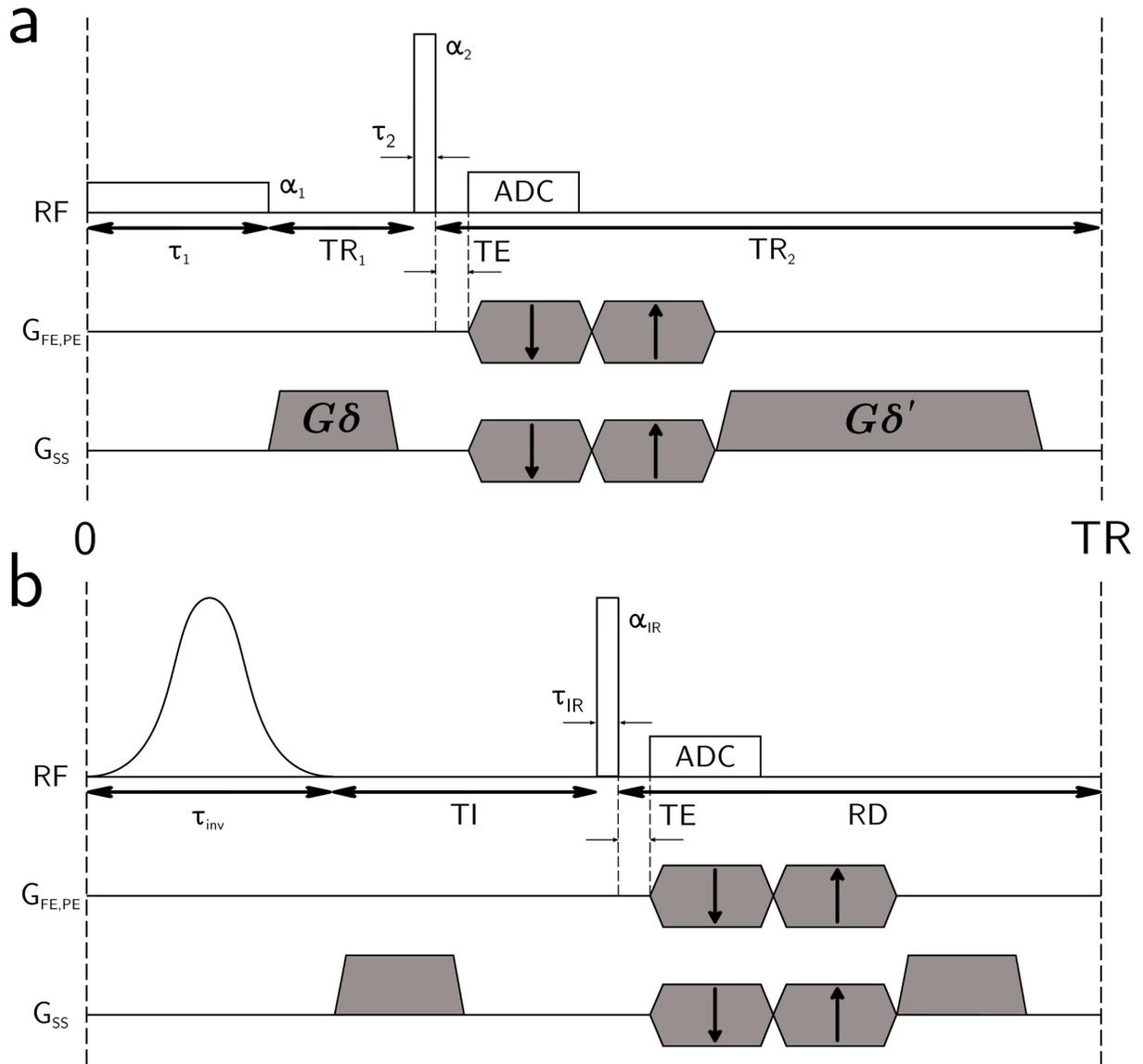


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| Component | Short- T_2 | Long- T_2 |
|----------------------------|---|---------------------------|
| Parameters | $T_1^S (\searrow), T_2^S (\nearrow)$ | T_1^L, T_2^L, D |
| RF Pulses | $\alpha_1 (\searrow), \alpha_2$ $\tau_1 (\nearrow), \tau_2 (\searrow)$ | α_1, α_2 — |
| Gradients influence | — | $G\delta, G\delta'$ |
| Adiabatic inversion effect | saturation | inversion |

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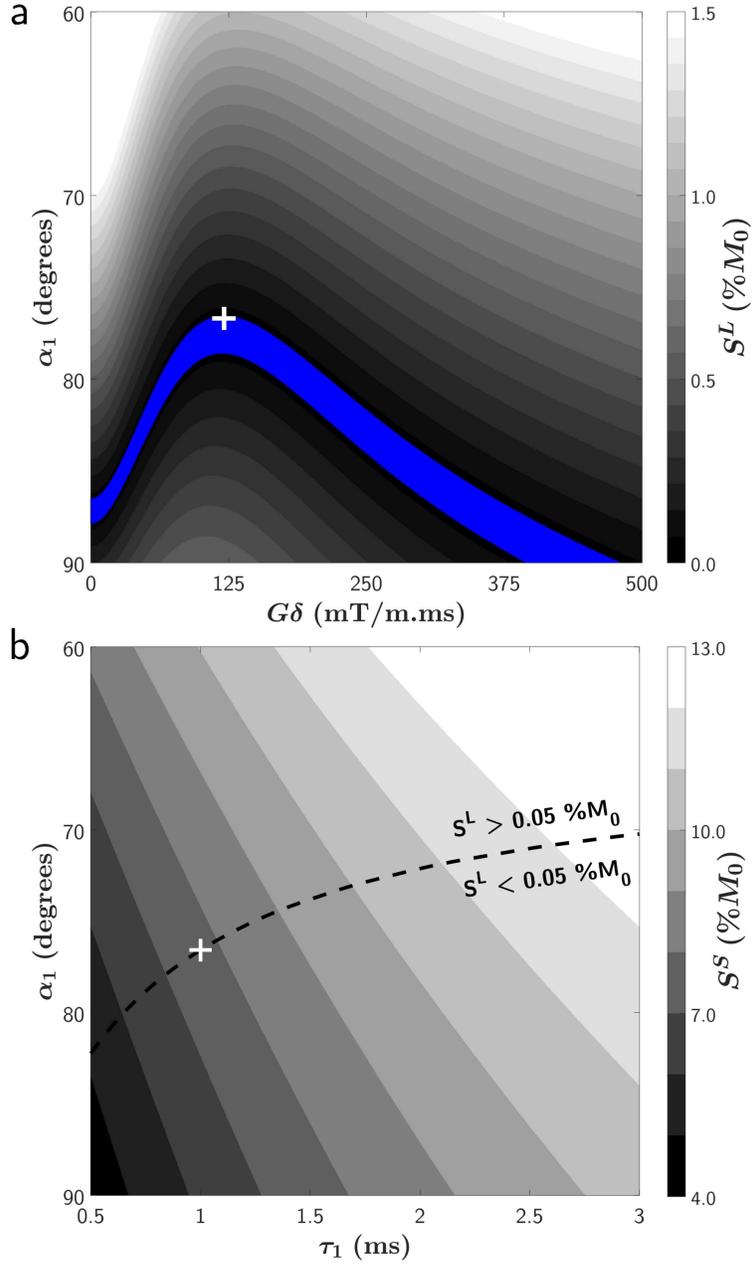


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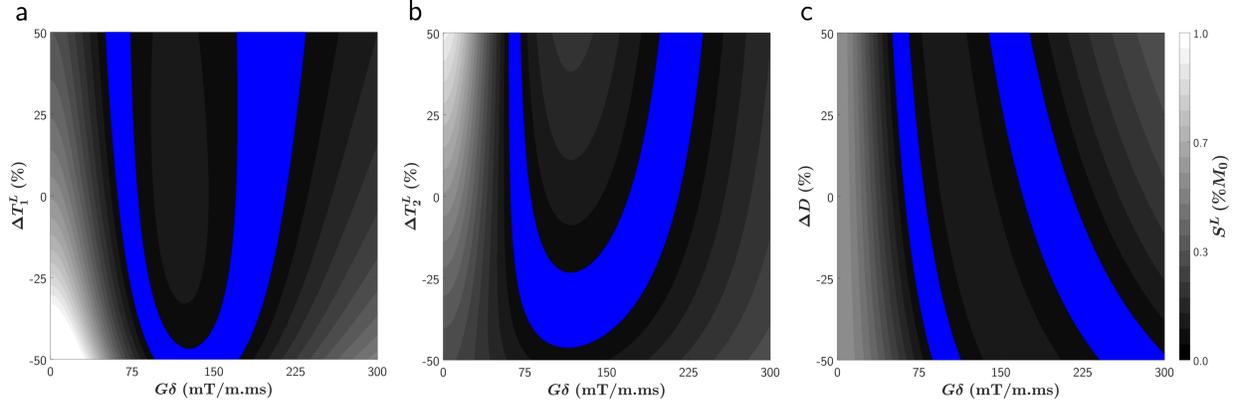


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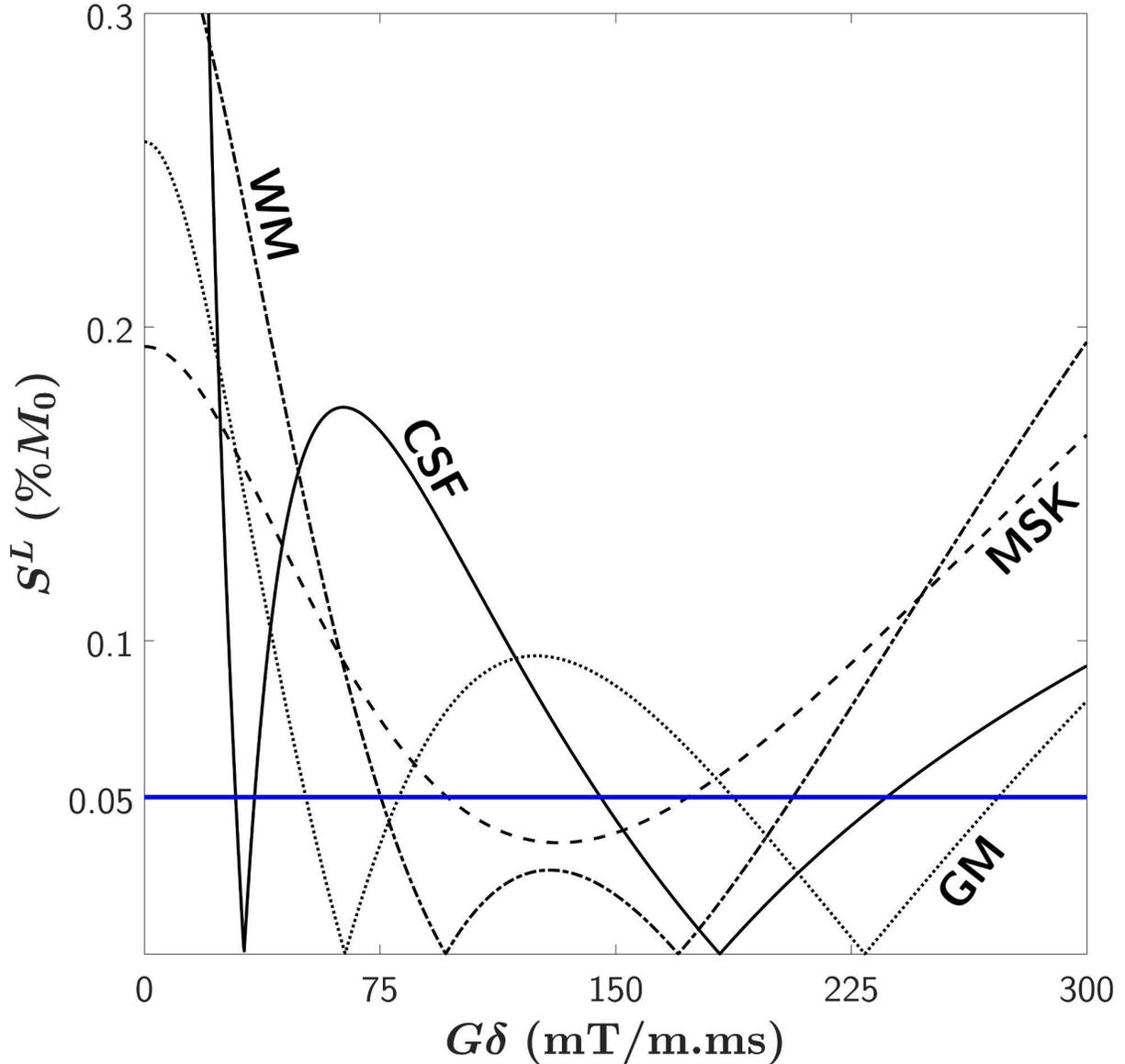


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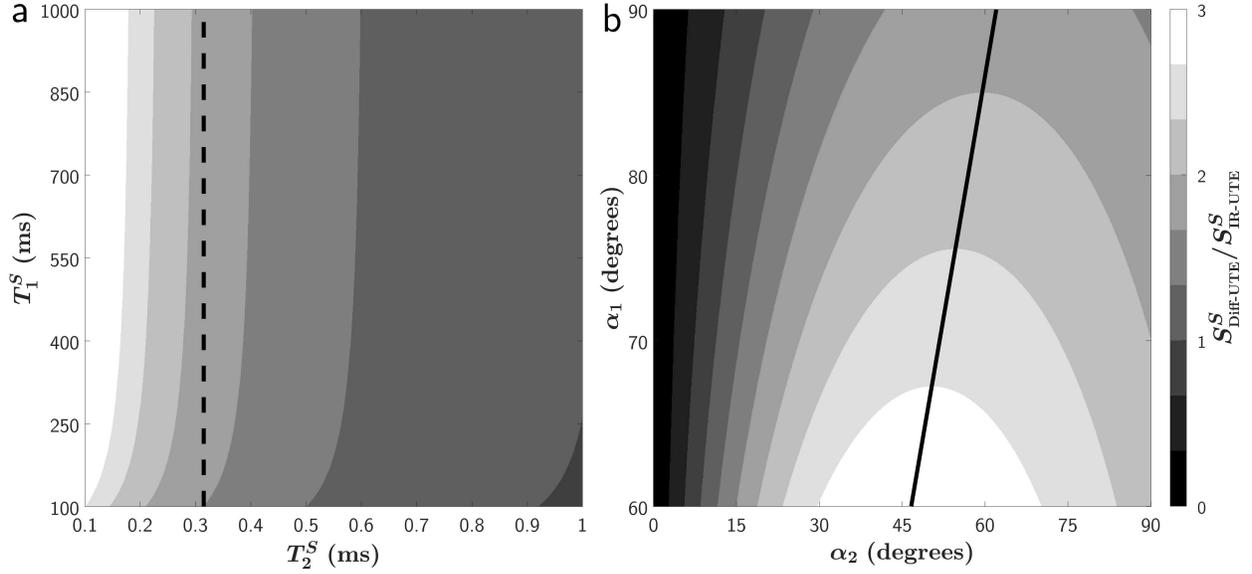


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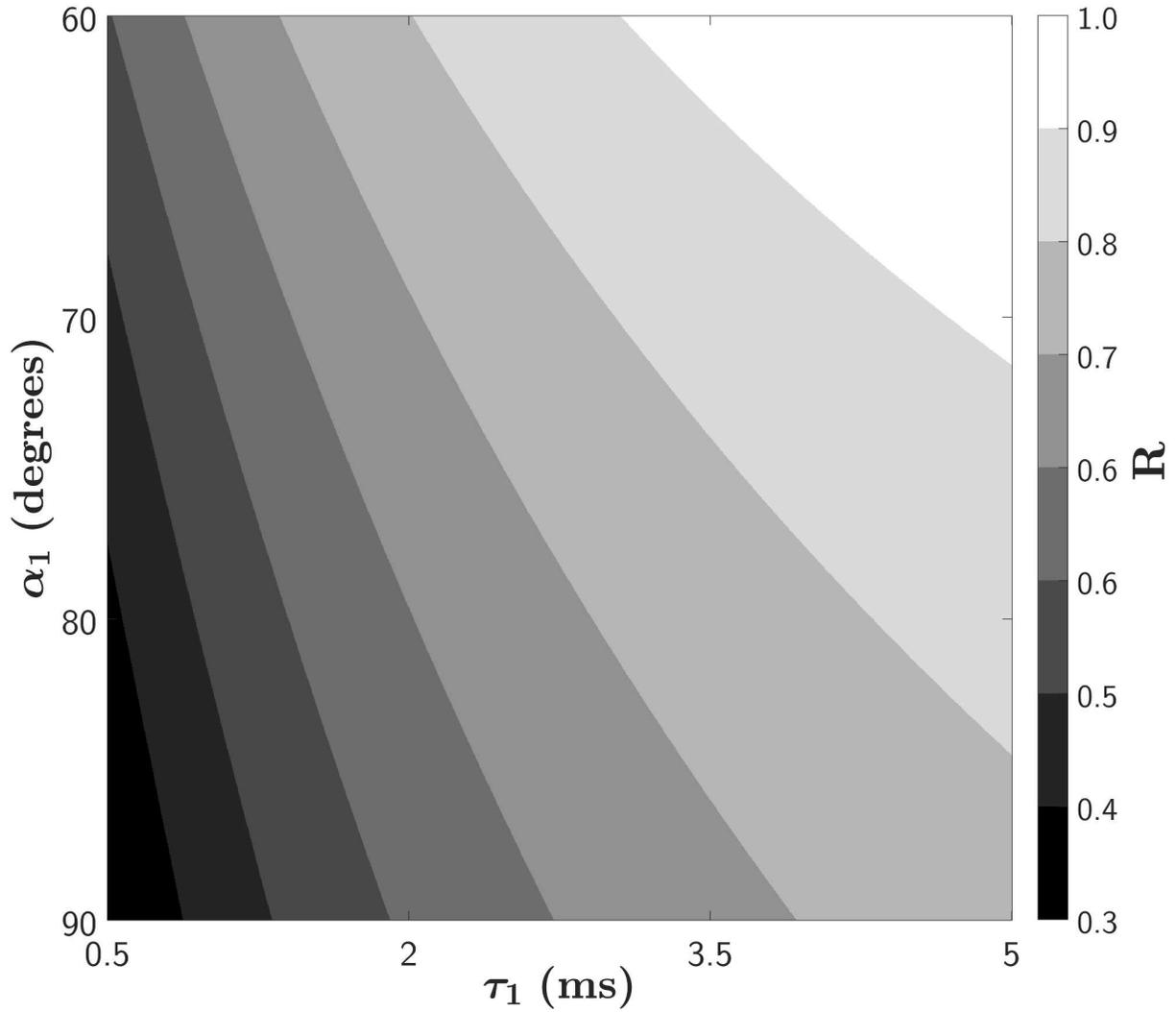


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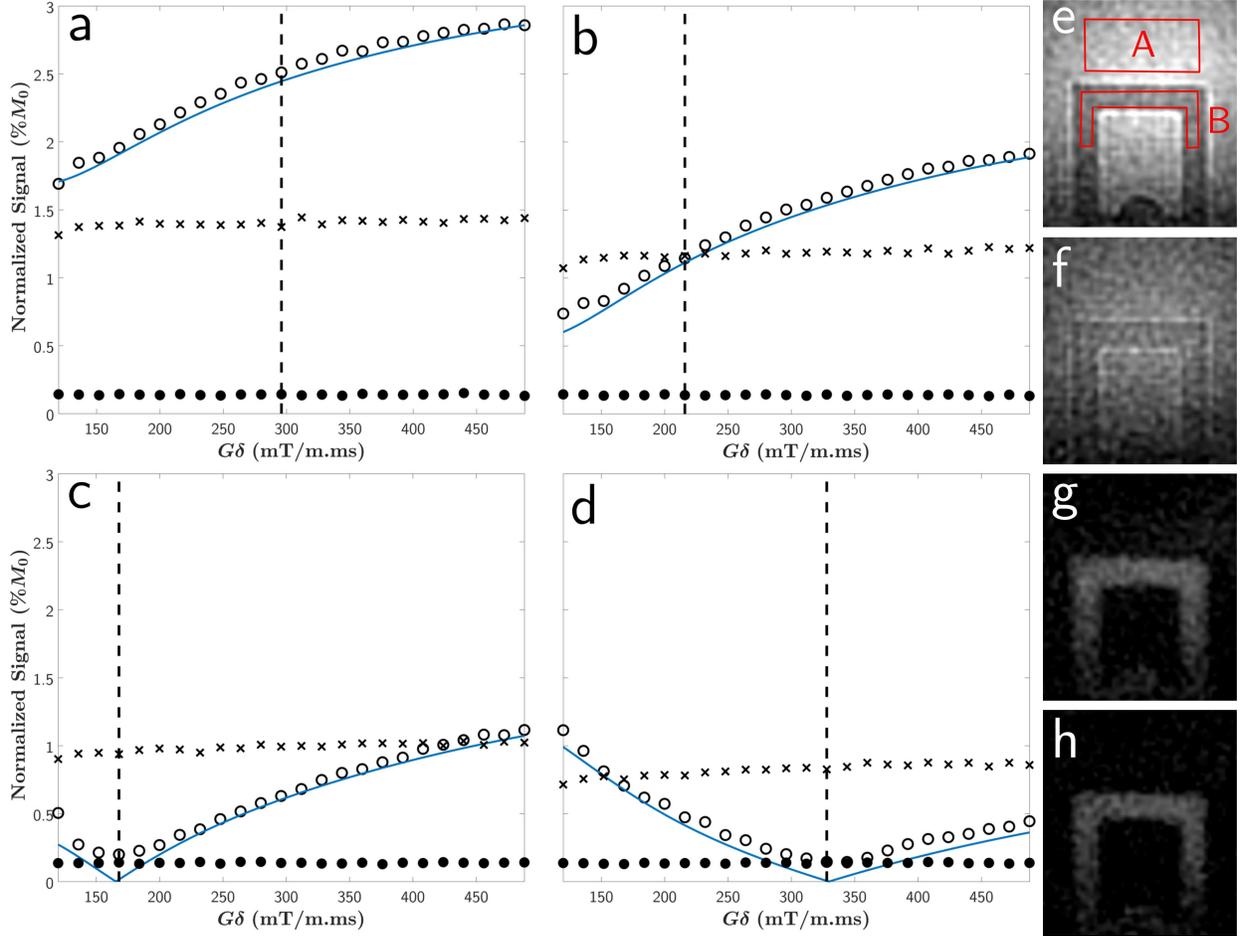


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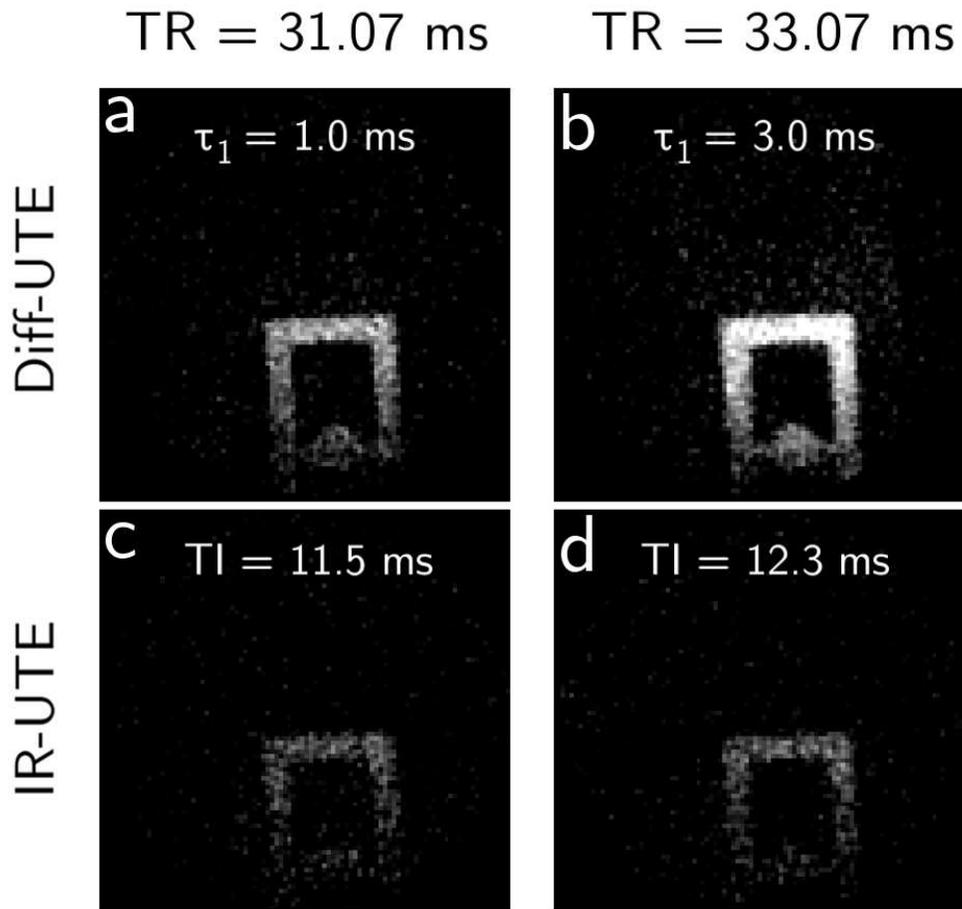


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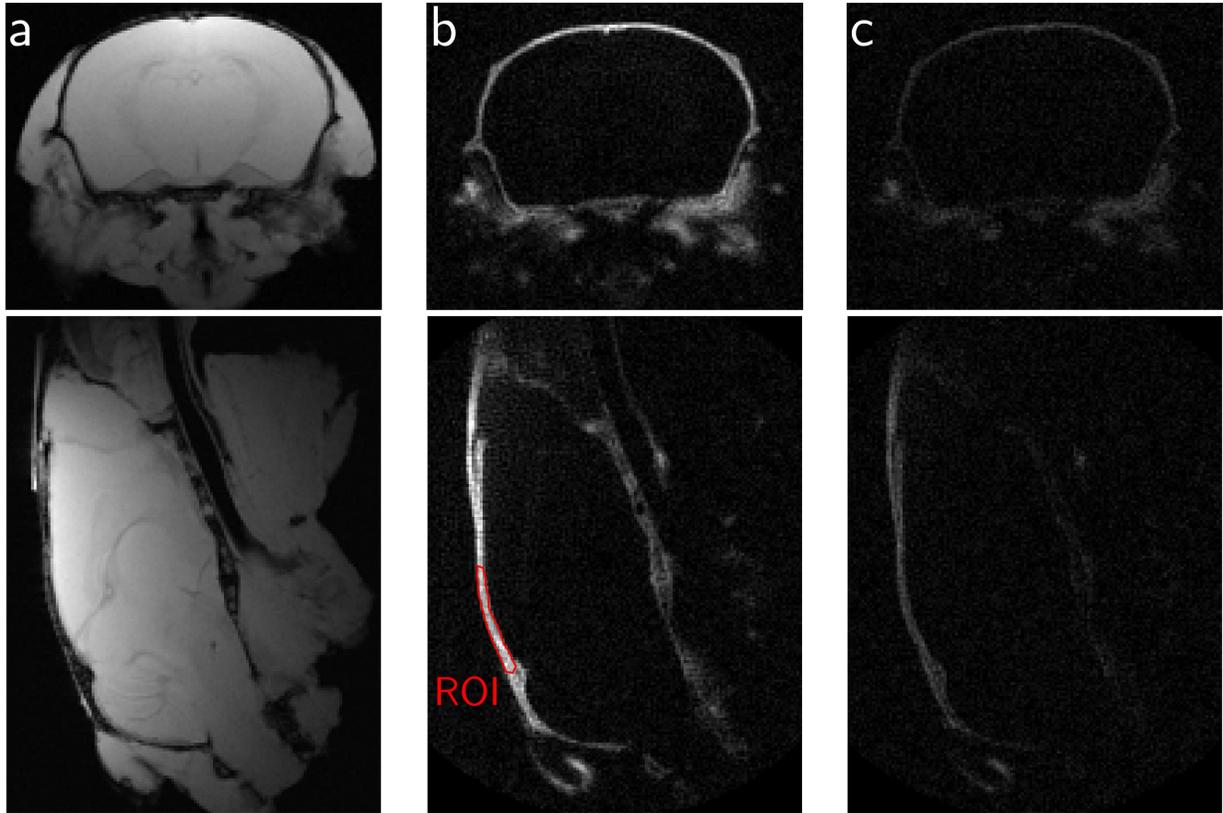


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