Clinically compatible subject-specific dynamic parallel transmit pulse design for homogeneous fat saturation and water-excitation at 7T: Proof-of-concept for CEST MRI of the brain

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Purpose: To evaluate the benefits and challenges of dynamic parallel transmit (pTx) pulses for fat saturation (FS) and water-excitation (WE), in the context of CEST MRI.

Methods: “Universal” kT-points (for FS) and spiral non-selective (for WE) trajectories were optimized offline for flip angle (FA) homogeneity. Routines to optimize the pulse shape online, based on the subject’s fields maps, were implemented (target FA of 110°/0° for FS, 0°/5° for WE at fat/water frequencies). The pulses were inserted in a CEST sequence with a pTx readout. The different fat suppression schemes and their effects on CEST contrasts were compared in 12 volunteers at 7T.

Results: With a 25% shorter pulse duration, pTx FS largely improved the FA homogeneity (root-mean-square-error (RMSE) = 12.3° vs. 53.4° with circularly-polarized mode, at the fat frequency). However, the spectral selectivity was degraded mainly in the cerebellum and close to the sinuses (RMSE = 5.8° vs. 0.2° at the water frequency). Similarly, pTx WE showed a trade-off between FA homogeneity and spectral selectivity compared to pTx non-selective pulses (RMSE = 0.9° and 1.1° at the fat and water frequencies, vs. 4.6° and 0.5°). In the brain, CEST metrics were reduced by up to 31.9% at −3.3 ppm with pTx FS, suggesting a mitigated lipid-induced bias.

Conclusion: This clinically compatible implementation of dynamic pTx pulses improved the fat suppression homogeneity at 7T taking into account the subject-specific B₀ heterogeneities online. This study highlights the lipid-induced biases on the CEST z-spectrum. The results are promising for body applications where B₀ heterogeneities and fat are more substantial.

KEYWORDS
7T MRI, CEST, dynamic pulse design, fat saturation, fat suppression, parallel transmission, water-excitation

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1 INTRODUCTION

Chemical Exchange Saturation Transfer (CEST) MRI can provide whole-brain metabolic maps, with potentially high clinical value.\(^1\) By means of a saturation pulse train applied at the resonance frequency of the metabolite followed by an image at the water frequency, the magnetization transfer from the saturated metabolite pool to the free water pool can be quickly quantified and the metabolite concentration and exchange rate (or related metrics) can be derived. The Amide Proton Transfer (APT) maps, one of the most promising CEST contrast, for example showed diagnostic capabilities of brain tumors comparable to post-contrast imaging, with fine depiction of the edema, and the potential to non-invasively detect pH changes, which is of particular interest to evaluate the viability of the ischemic penumbra in acute stroke.\(^2-4\) The first obstacles for the clinical translation of CEST are the low Signal-to-Noise Ratio (SNR) and peak amplitudes of the metabolites of interest, which result in long acquisition times, low resolution or reduced field-of-view. However, these obstacles can be overcome with higher field strengths and the recent clinical approval of 7T MR systems motivate further the development of CEST at 7T for clinical use.

But at 7T other challenges arise. The increased transmit field (\(B_0^+\)) heterogeneities because of the reduced wavelength, mitigate the efficiency of fat suppression RF pulses, while fat lipids are generally detrimental to CEST. Due to the chemical shift with respect to free water, fat can cause artifacts in the images (e.g., aliasing) and/or bias the measurements. As already described in the literature,\(^5-7\) the z-spectrum amplitude is reduced in the presence of lipids in phase with water and reversed peaks can appear when lipid and water are out-of-phase. Moreover, the lipids’ contribution to the z-spectrum is asymmetric, with the main fat peaks around \(−2.7, −3.3,\) and \(−3.8\ ppm.\(^8,9\) This directly affects the quantification accuracy of APT around 3.5 ppm when calculating the asymmetry with respect to 0 ppm. It also affects the quantification of the relayed-Nuclear Overhauser Effects (rNOE) attributed to aliphatic and olefinic protons,\(^5\) which overlaps with fat peaks (\(−5\ to 0\ ppm).\)

In the head, lipids are mainly found in the scalp, which can cause aliasing, chemical-shift and/or N/2-ghosting artifacts, and to a lower extent, in the white matter. However, there is also an increasing interest to apply CEST in body regions such as the breast\(^7\) or the knee where lipids are much more abundant and where an efficient fat suppression robust to \(B_0\) heterogeneities is essential.

This is even more critical at 7T where \(B_0\) heterogeneities are increased, hindering the efficiency of the commonly used binomial water-selective pulses,\(^9\) adding up to the challenges at 7T. Post-processing methods specific to CEST have been proposed to correct for fat-induced artifacts based on the residual signal in the water-saturated image,\(^7\) but this method relies on the assumption that the lipids are not saturated, which is not the case for the rNOE, and prevents a reliable multi-pool Lorentzian fitting for the metrics quantification.

Parallel transmission (pTx) of channel-specific pulse shapes increases the degrees of freedom to manipulate the \(B_1^+\) distribution.\(^10\) Dynamic pulses (temporally varying RF pulse shapes combined with simultaneously applied \(B_0\) gradients) additionally increase these degrees of freedom to improve the flip angle (FA) homogeneity. Dynamic pulses were also demonstrated to have the ability to provide simultaneous spatial and spectral selectivity (“spatial-spectral pulses”).\(^11\) Based on this finding, Zhao et al.\(^12\) proposed an optimization method to design pulses selective both in the 3D space and along the frequency axis, for fat saturation, taking into account \(B_0\) heterogeneities at 3T. The pulse shape was first calculated using the small-tip-angle approximation and then linearly scaled to 90°. Promising results were obtained, but several parameters were empirically determined, limiting the clinical translation, and evaluations were only performed in one healthy volunteer.

In this study, we elaborated on this approach to design dynamic pTx pulses for fat saturation and water-selective excitation (hereafter referred as water-excitation) in a clinically compatible framework at 7T. To gain accuracy, Bloch simulations were used for fat saturation pulses in lieu of the linearly scaled small-tip-angle approximation. To save computational time at the acquisition, “universal”\(^13\) transmit-k-space trajectories were determined offline beforehand on a cohort of subjects and the final pulse shape was optimized online based on the subject’s \(B_0\) and \(B_1^+\) data. The feasibility, potential benefits and pitfalls of this approach were evaluated in the context of CEST MRI of the brain, where partial volume effects and interfaces with fat tissue are restrained compared to other body regions, allowing a proper inspection of the effects on the z-spectrum. This study builds on the homogeneous CEST saturation pulse train previously implemented for the brain at 7T with complementary sets of phase difference between adjacent channels.\(^14\)

2 METHODS

This study was performed after institutional review board approval and written informed consent was obtained from each participant.
2.1 Pulse design

The initial CEST protocol consisted of a semi-static pTx saturation module with two interleaved complementary sets of phase difference between adjacent channels (shown to increase the spatial homogeneity of the saturation in the brain at 7T) and a spiral-centric-reordered-square readout with online-customized pTx excitation pulses based on a “universal” spiral non-selective (SPINS) transmit trajectory. This whole-brain protocol demonstrated an improved reproducibility compared to protocols with circularly-polarized (CP) saturation and excitation.

Two widely used fat suppression approaches were considered:

1. A fat saturation pulse before the readout (after the CEST preparation).
2. Water-selective excitation pulses in the readout (in place of the pTx non-selective excitation pulses).

For approach 1, the standard of reference was a CP Gaussian pulse (FA = 110°, duration = 6120 μs, frequency = −3.3 ppm). It was compared to a dynamic pTx pulse based on a “universal” kT-points trajectory with a 25% shorter duration (4550 μs) to mitigate sensitivity to B₀ heterogeneities. The kT-points coordinates and sub-pulse durations were determined through a global search (MATLAB 2017b, The MathWorks, Natick, MA) with an interior point solver minimizing the root-mean-square-error (RMSE) on the resulting FA in a healthy population (10 women, 10 men, same cohort as for the determination of the SPINS trajectory). This offline optimization was initially performed for an inversion pulse (target FA = 180°); because little variation is expected for a target FA of 110°, the determined kT-points were kept unchanged. Next, the sub-pulse amplitudes and phases were optimized at the acquisition based on the subject’s B₀ and B₁⁺ data with the previously determined kT-points (Figure 1A). For this online optimization, the FA RMSE in the brain was minimized with a target of 110° at −3.3 ppm (main fat frequency) and 0° at 0 ppm (water frequency). The brain mask was derived from the B₁⁺ map of the CP mode, excluding voxels with intensities lower than the 10th percentile, followed by a morphologic opening (erosion and dilation) with a 5-voxel-radius sphere. An increase of up to 30% of the maximum local Specific Energy Dose (SED) (energy absorbed per mass of tissue, which is proportional to the specific absorption rate) of the readout (including the fat saturation pulse) was allowed compared to the value for the readout of reference (CP-mode fat saturation with online customized non-selective pTx excitation pulses).

For approach 2, the readout excitation pulses were replaced by water-excitation pulses with the same universal SPINS trajectory (Figure 1B). The water-selectivity was achieved during the subject-specific online optimization, with a target of 5° at 0 ppm and 0° at −3.3 ppm. For this optimization, the limit on the readout SED increase was set to 32% of the readout of reference instead of 30% for approach one because the performances were very limited when forcing a limit of 30%.

For comparison purposes, the pulse design and associated FA map predictions were additionally performed for both approaches (fat saturation and water-excitation) imposing an SED limit equal to the SED value of the readout of reference (CP-mode fat saturation with non-selective pTx excitation).

2.2 In vivo data acquisition

The experiments were performed on a 7T whole-body system (Terra, Siemens Healthcare, Erlangen, Germany) with an 8Tx/32Rx brain coil (Nova Medical). The overall protocol (described in Table 1) consisted of an anatomic MPRAGE image, B₁⁺ mapping in CP and CP²⁺ mode and a whole-brain CEST protocol performed at tw B₁ levels with each of the 4 fat suppression schemes: no fat suppression, fat saturation in CP mode, pTx fat saturation with kT-points trajectory, pTx water-excitation with SPINS trajectory. For all schemes, the readout excitation pulses were the same (non-selective pTx pulses with SPINS trajectory), except for the water-excitation scheme where the readout pulses were replaced by the pTx water-excitation pulses. The subject-specific pTx optimizations did not add time to the protocol because they could be performed during the anatomic image acquisition.

The initial CEST protocol with previously published parameters was first applied in healthy volunteers (ages 40.3 ± 8.3 years old, 3 women, 3 men). However, for these parameter values (TE = 1.43 ms), the main fat peak at −3.3 ppm (targeted in the pulse design) was in opposite phase with water, which made the interpretation of the z-spectrum non-trivial. Therefore, the same protocol with a shorter TE (1.03 ms) was acquired in another group of 6 healthy volunteers (ages 33.5 ± 6.7 years old, 2 women, 4 men) to have the fat peak at −3.3 ppm in phase with water. To achieve this TE, the receiver bandwidth had to be tripled (from 660 to 1930 Hz/pixel), which was not optimal regarding SNR, but was sufficient to observe the effects of the fat suppression pulses on the z-spectrum averaged across large regions.

The parameters specific to the CEST preparation were listed in Table 2.
| **Table 1** Complete acquisition protocol parameters |
|-----------------------------------------------------|
| **General parameters** | **Specific parameters** | **pTx parameters** |
| **Anatomic image** | 3D sagittal MPRAGE, FOV = 240×240×192 mm³, resolution = 0.75×0.75×0.75 mm³, TR = 3700 ms, TE = 1.9 ms, IR = 1100 ms, GRAPPAphase = 2, GRAPPAslice, FA = 5°, BW = 240 Hz/pixel, AD = 5 min 00s | Compressed sensing; under-sampling factor = 4.0, density = 0.50, jitter radius = 1.2, samples/TR = 200, no. of reference lines = 32, no. of iterations = 15 Online customization of the excitation pulse with the “universal” SPINS trajectory |
| **B₁ map in CP mode** (used for correction of CEST data) | 2D pre-saturated sagittal turbo-FLASH, FOV = 230×230 mm², 72 slices, resolution = 2.4×2.4 mm², slice thickness = 2.5 mm, gap = 0.5 mm, TR = 16270 ms, TE = 1.82 ms, GRAPPAphase = 2, FA = 5°, BW = 450 Hz/pixel, AD = 34 s | 45°-phase difference between transmit channels (circularly polarized (CP) mode) |
| **B₁ map in CP₂⁺ mode** (used for correction of CEST data) | (Same as previous line) | 90°-phase difference between transmit channels (CP₂⁺ mode) |
| **CEST protocol without fat suppression** | 3D sagittal, FOV = 230×230×173 mm³, resolution = 2.4×2.4×2.4 mm³, TR = 3.7 ms, FA = 5°, PFphase = 6/8, PFslice = 6/8, GRAPPAphase = 3, GRAPPAslice = 2, AD = 6 min 14 s (for each B₁ saturation level), TE = 1.43 ms and BW = 660 Hz/pixel for the first group of participants, TE = 1.03 ms and BW = 1930 Hz/pixel for the second group | • MIMOSA¹⁴ semi-static pTx mode for CEST saturation • Readout elongation = 0.1, Elliptical scanning • Protocol repeated with two B₁ saturation levels All CEST preparation parameters are described in Table 2. Online customization of (non-water-selective) excitation pulses with the “universal” SPINS trajectory |
| **CEST protocol with CP-mode fat saturation** | (Same as previous line) + CP-mode Gaussian fat saturation pulse (FA = 110°, duration = 61.20 μs) | (Same as previous line) (Same as previous line) |
| **CEST protocol with dynamic pTx fat saturation** | (Same as for CEST protocol without fat suppression) | (Same as previous line) Online customization of (non-water-selective) excitation pulses with the “universal” SPINS trajectory + online customization of the fat saturation pulse with the “universal” k₇-points trajectory |
| **CEST protocol with dynamic pTx water-excitation** | (Same as previous line) | (Same as previous line) Online customization of water-selective excitation pulses with the “universal” SPINS trajectory |

Note: GRAPPAphase, GRAPPAslice, PFphase, PFslice: Generalized Autocalibrating Partial Parallel Acquisition factor and Partial Fourier factors along the phase- and slice-encoding axes respectively. For the parameters specific to the CEST preparation, see Table 2.

Abbreviations: pTx, parallel transmission; FA, readout flip angle; AD, acquisition duration; FOV, field of view; TR, repetition time; TE, echo time; IR, inversion time; BW, readout bandwidth; MPRAGE, Magnetization Prepared Rapid Acquisition Gradient Echo; FLASH, Fast Low Angle Shot; no.: number.
### TABLE 2  
**CEST preparation module and model fitting parameters**

#### CEST preparation module parameters

| Parameter                                    | Description                                                                 |
|----------------------------------------------|-----------------------------------------------------------------------------|
| Transmit mode for CEST saturation            | Semi-static pTx mode MIMOSA\(^{14}\): tw interleaved complementary sets of phase difference between adjacent channels |
| No. of saturation pulses                     | 120                                                                         |
| Pulse type                                   | Gaussian                                                                    |
| Pulse duration                               | 15.36 ms                                                                   |
| Inter-pulse delay                            | 10 ms                                                                       |
| Average single-pulse B\(_1\) levels          | 0.72 μT, 1.00 μT                                                            |
| Average pulse train B\(_1\) levels (B\(_1\)\(_\text{RMS}\)) | 0.67 μT, 0.93 μT                                                           |
| No. of offsets                               | 56                                                                          |
| Offsets (ppm)                                | −300, −100, −50, −20, −12, −9, −7.25, −6.25, −5.5, −4.7, −4, −3.3, −2.7, −2, −1.7, −1.5, −1.1, −0.9, −0.6, −0.4, 0, 0.4, 0.6, 0.95, 1.1, 1.25, 1.4, 1.55, 1.7, 1.85, 2, 2.15, 2.3, 2.45, 2.6, 2.75, 2.9, 3.05, 3.2, 3.35, 3.5, 3.65, 3.8, 3.95, 4.1, 4.25, 4.4, 4.7, 5.25, 6.25, 8, 12, 20, 50, 100, −300 |
| Normalization image (\(M_0\)) recovery time  | 12 000 ms                                                                   |
| Recovery time between offsets                | 1000 ms                                                                     |

#### CEST model fitting parameters: 5-pool Lorentzian function

|                       | Initial value | Lower bound | Upper bound |
|-----------------------|---------------|-------------|-------------|
| Offset                | 1             | 0.6         | 1           |
| **Water**             |               |             |             |
| Amplitude             | 0.9           | 0.02        | 1           |
| Peak width (ppm)      | 1.4           | 0.3         | 10          |
| Peak position (ppm)   | 0             | −1          | 1           |
| **Amide**             |               |             |             |
| Amplitude             | 0.025         | 0           | 0.2         |
| Peak width (ppm)      | 0.5           | 0.4         | 4           |
| Peak position (ppm)   | 3.5           | 3           | 4           |
| **rNOE**              |               |             |             |
| Amplitude             | 0.02          | 0           | 0.6         |
| Peak width (ppm)      | 3             | 0.5         | 10          |
| Peak position (ppm)   | −3.5          | −4          | −2.5        |
| **Semi-solid MT pool**|               |             |             |
| Amplitude             | 0.1           | 0           | 1           |
| Peak width (ppm)      | 25            | 10          | 99          |
| Peak position (ppm)   | −2            | −4          | 0           |
| **Amine**             |               |             |             |
| Amplitude             | 0.01          | 0           | 0.5         |
| Peak width (ppm)      | 1             | 1           | 3.5         |
| Peak position (ppm)   | 2.2           | 1.7         | 2.5         |

Abbreviations: B\(_1\)\(_\text{RMS}\), B\(_1\) root-mean-square; rNOE, relayed-Nuclear Overhauser Effects; MT: Magnetization Transfer.
FIGURE 1 Top: optimal “universal” transmit k-space trajectory determined on a population of 20 healthy volunteers for the design of dynamic parallel transmit (pFx) pulses for fat saturation using 6 k_τ-points (A) and water-selective excitation using a SPINS trajectory (B). Bottom: example of final pulse shape (amplitude and phase along time in different colors for each of the 8 channels) obtained after online customization based on the B_0 and B_1+ data of the subject (HV4 in Figure 3). The gradient trajectories along the readout (GRO), phase (GPE) and slice (GSS) encoding axes are also illustrated.

2.3 Data analysis

For each fat suppression scheme and each TE, acquired CEST data were corrected for motion along time using Statistical Parametric Mapping (SPM12) and for voxel-wise B_0 offset (water peak registration), and normalized by the baseline signal at −300 and 300 ppm. The Magnetization Transfer Ratio asymmetry (MTR_{asym}) was calculated voxel-wise at −2.7, −3.3, −3.5, and −4.7 ppm, according to the following formula to obtain positive values given the low B_1 saturation level used:

\[
MTR_{asym}(\Delta \omega) = \frac{M(-\Delta \omega) - M(\Delta \omega)}{M_0},
\]  

with \( \Delta \omega \) the offset, \( M(\Delta \omega) \) the signal magnitude at offset \( \Delta \omega \) and \( M_0 \) the normalization baseline signal magnitude. These maps were then registered to the Montreal-Neurological-Institute template and structural atlas (1 mm-isotropic) using ANTs with an affine registration to the anatomic image before a non-linear registration of the anatomic image to the template. The warping fields from the CEST to the template space were applied to the MTR_{asym} maps and the predicted FA maps for every pulse. The mean MTR_{asym} and FA maps across subjects were computed in the template space.

To evaluate the effects of the different fat suppression schemes, the z-spectrum was plotted in the upper
brain white (WM) and gray matter (GM), where fat aliasing artifacts are typically observed, as well as in the scalp, where the fat concentration is higher. To generate these regions-of-interest (ROIs), the segmentation of brain tissues was performed on the anatomic image using SPM12 with 6 classes. The scalp ROI was obtained by averaging the scalp segmentation across subjects, excluding voxels with occurrence lower than 0.7 and inferior to the corpus callosum.

The effects on the CEST metrics of each fat suppression scheme were evaluated looking at the differences with respect to the acquisition without fat suppression in different brain regions defined by the atlas. The mean predicted FA of each pulse (from simulations) in those regions was also quantified.

Finally, to assess the effects of the different fat suppression schemes on the quantification of the main metabolites, a 5-pool Lorentzian fitting was applied after B1+ correction of the saturation pulse train and denoising, to measure the peak amplitudes for APT, rNOE, Magnetization-Transfer (MT), and amine contrasts. The parameters used for the model fitting were described in Table 2.

3 RESULTS

3.1 Pulse design

As can be observed on the predicted FA maps (Figure 2), a successful design of water-selective (compared to the pTx non-selective pulses) and fat saturation pulses (compared to CP-mode fat saturation pulses) with improved FA homogeneity or spectral selectivity was obtained with the proposed implementation. However, the FA maps (Figure 2, 2nd and 5th rows) obtained when restricting the SED to the value of the readout of reference (4th row) showed very limited improvements with FA drops in the lower and upper brain for pTx water-excitation and large FA heterogeneities and inaccuracies for pTx fat saturation, demonstrating the need to allow an SED increase in the pulse design to obtain decent performances.

For pTx water-excitation with increased SED (32% increase), the spectral selectivity of water was achieved with a predicted FA of $0.82\pm0.05^\circ$ at the fat frequency compared to $4.54\pm0.14^\circ$ for the pTx non-selective pulses and $0.92\pm0.06^\circ$ for the pTx water-excitation with non-increased SED (mean ± standard deviation across
FIGURE 3  Subjects' distribution of the predicted flip angle (FA) mean value in different brain regions for each pulse at the main fat frequency (−3.3 ppm) and at the water frequency. The target FA is indicated by the horizontal yellow line for each pulse. In this box-and-whisker plot, the black line represents the median, the box extends vertically from the 1st to the 2nd quartile, the whiskers extend from the box to 1.5 times the vertical box length (interquartile range) and fliers (empty circles) are points beyond the whiskers. (*): pulse design performed imposing a Specific Energy Dose (SED) limit on the total readout equal to the SED of the readout obtained with circularly polarized (CP)-mode fat saturation and parallel transmit (pTx) non-selective excitation (instead of allowing a 30% and 32% increase for pTx fat saturation and pTx water-excitation, respectively).

Subjects of the average FA in the brain). However, the FA homogeneity was degraded at the water frequency with an average RMSE of 1.1° (22.6%) versus 0.5° (10.1%) for non-water-selective pulses. The FA reduction mainly occurred in the lower part of the brain. Nevertheless, it was still improved compared to the CP-mode SED constrained version (average RMSE of 1.3°, or 26.2%).

As for fat saturation, pTx pulses with 30% SED increase highly improved the FA homogeneity at the fat frequency (average RMSE = 12.3° (11.2%) vs. 53.4° (48.6%) for the CP fat saturation and 48.1° (43.8%) for the non-increased SED version), but slightly degraded the spectral selectivity compared to CP fat saturation (average FA of 3.14° ± 0.96° vs. 0.17° ± 0.02° at the water frequency). These high residual FAs were mainly observed in the cerebellum and in the vicinity of the sinuses. Allowing a 30% SED increase also helped the spectral selectivity (average FA of 5.50 ± 1.07° for the non-increased SED version at the water frequency).

The predicted FA for each of those pulses were quantified by brain regions in Figure 3 to further characterize the water spectral selectivity of the pTx water-excitation and the improved FA homogeneity and accuracy of the pTx fat saturation pulses. The thalamus, at the center of the brain was the region with the most accurate FA, whereas the cerebellum, at the lowest end of the brain, was the region with the highest FA drop-out and the most challenging to address. Regarding pTx water-excitation, only moderate improvement could be obtained when increasing the SED limit compared to the readout of reference (CP-mode fat saturation and non-selective pTx excitation). Those improvements were in the order of 10%, mainly in the cerebellum. However, for pTx fat saturation, a significant improvement of the FA homogeneity and accuracy could be obtained when increasing the SED limit, with no region below 90°, unlike with the CP-mode fat saturation or the pTx fat saturation with CP-mode SED limit. These improvements were in the order of 138% in the cerebellum, 100% in the parietal lobe, and 36% in the WM, for example. The FA distribution range was also largely reduced with pTx, providing a higher reproducibility across subjects. The spectral selectivity of the pTx fat saturation improved when allowing 30% SED increase, but the RMSE at the water frequency remained much higher than in CP mode (5.8° vs. 0.2° in average in the brain with CP mode).
3.2 Effects on CEST metrics

3.2.1 Effects on z-spectrum

Figure 4 compares the z-spectrum obtained with all 4 fat suppression schemes with each CEST protocol: (A) the standard protocol with a TE of 1.43 ms resulting in an opposite phase relation between water and the main fat peak at −3.3 ppm, targeted in the pulse design, and (B) the modified protocol with a TE of 1.03 ms (and tripled bandwidth) resulting in an in-phase relation at −3.3 ppm. As described in the Introduction, whether fat is in phase or in opposite phase with the water can have a large impact on the z-spectrum. Therefore, to help interpretation, this information has been added in the background of Figure 4: the background is brighter at offsets in-phase with water and darker at offsets in opposite phase (given the particular TE of the pr). The difference of each fat suppressed acquisition with respect to the acquisition without fat suppression was also plotted in dotted line. Table 3 summarizes the main effects observed in the upper WM and GM and in the scalp where a higher lipid content is expected.

For TE = 1.43 ms, because the fat frequency targeted by the fat suppression pulses was in opposite phase with water, the corresponding fat signal might already have been mitigated and consequently, the main effects were observed at the closest in-phase fat frequency, −2.7 ppm, with an increase in the scalp of +5.5% with pTx fat saturation and +1.4% with CP-mode fat saturation and pTx water-excitation (+2.3% in the upper WM and GM with pTx fat saturation). At −3.3 ppm, a decrease of approximately −1.3% was observed in the scalp only, with all fat suppression schemes, which is in agreement with an expected z-spectrum increase in the case of fat in opposite phase with water.

For TE = 1.03 ms, the effects of the fat suppression pulses at the targeted fat frequency were much easier to interpret. At −3.3 ppm, in the scalp, the z-spectrum was increased by +11.8%, +20%, and +6.2% with CP-mode fat saturation, pTx fat saturation, and pTx water-excitation, respectively. In the upper WM and GM, these effects were lower because of the lower lipid content, but still clearly noticeable: +1%, +2.4%, and +1.4%, respectively. Interestingly, the overall baseline also appeared reduced by 2%-4% in the scalp with all fat suppression schemes, potentially because of decreased semi-solid MT effects with the reduced fat contribution.

Additionally, for both TEs and with all fat suppression schemes, in the scalp, the z-spectrum amplitude (as can representatively be measured at 0 ppm) was increased by up to 46.9% with pTx fat saturation, compared to the acquisition without fat suppression, showing the detrimental effect of fat for CEST.

3.2.2 Effects on MTR asymmetry quantification

The corresponding whole-brain MTR asym maps are presented in Figure 5 for each fat suppression scheme (sagittal and coronal views are displayed in Supporting Information Figures S1-S4). The main differences were observed in the scalp at −2.7 ppm for TE = 1.43 ms and at −3.3 and −3.5 ppm for TE = 1.03 ms. Values were reduced in all fat suppressed acquisitions, but more efficiently and homogeneously with pTx fat saturation where the MTR asym in the scalp were close to 0 particularly at −3.3 and −3.5 ppm for TE = 1.03 ms (targeted fat frequency and water in phase). Moreover, an improved homogeneity of the CEST contrast was observed with pTx fat saturation in the anterior brain at −2.7 ppm for TE = 1.43 ms and in the posterior brain at −3.3 and −3.5 ppm for TE = 1.03 ms (red dotted-line circles). At −4.7 ppm, the only noticeable difference appeared for the acquisitions with pTx fat saturation at TE = 1.43 ms, where the outer dura showed increased values (red arrow).

These differences in MTR asym with respect to the acquisition without fat suppression were quantified by brain regions in Figure 6. At TE = 1.43 ms, the main effects on the MTR asym values were seen at −2.7 ppm (offset in phase with water) in the frontal and parietal lobes, with reductions by approximately −4.4% and −6.5% with CP fat saturation, −25.7% and −21.5% with pTx fat saturation and −8.8% and −8.7% with pTx water-excitation, respectively. At −3.3 and −3.5 ppm (offsets in opposite phase with water), the reduction was minimal. However, at TE = 1.03 ms, the effects were more compelling. At −3.3 ppm, MTR asym values were reduced by up to −20.7% with CP fat saturation, −31.9% with pTx fat saturation and −20.5% with pTx water-excitation, respectively. Similar effects were observed at −3.5 ppm. The frontal, occipital and parietal lobes were the most affected regions. Reductions in MTR asym values up to −8.2%, −11.0%, and −8.7% were also observed at −2.7 ppm at this TE with CP fat saturation, pTx fat saturation and pTx water-excitation, respectively.

Finally, an overall observation that is worth noting is that, every time the offset region was not in phase with water (e.g., at −3.3 and −3.5 ppm for TE = 1.43 ms or at −4.7 ppm for TE = 1.03 ms), the effects of fat suppression were mitigated and highly changed from one brain region to another (likely because of a reduced fat signal contribution in the unsuppressed acquisition), attesting...
**FIGURE 4** Mean z-spectrum across healthy volunteers (n = 6) in the upper white and gray matter (left) and in the scalp (right) obtained with each protocol: (A) when the fat peak at -3.3 ppm is in opposite phase with water (initial protocol parameters, TE = 1.43 ms, bandwidth [BW] = 660 Hz/pixel) and (B) when in phase (TE = 1.03 ms, BW = 1930 Hz/pixel). Because the phase relation between water and fat can have a strong impact on the z-spectrum, this information was added in the background to help interpretation: given the TE, the offsets in phase with water are indicated by a bright background and the background becomes darker as the frequency shifts closer to an opposed phase. The z-spectrum obtained with each fat suppression scheme is plotted with a different color in solid line and the corresponding difference ratio in percentage \(100 \times (Z_{\text{fat suppression scheme}} - Z_{\text{no fat suppression}})/Z_{\text{no fat suppression}}\) is plotted in dotted line (with the values indicated on the right-hand y-axis). The vertical purple line indicates the main fat frequency (-3.3 ppm), which was targeted in the pulse design.
FIGURE 5 Whole-brain Magnetization Transfer Ratio (MTR) asymmetry maps (transversal view) at −2.7, −3.3, −3.5, and −4.7 ppm obtained with each fat suppression scheme and with each protocol: (A) when the fat peak at −3.3 ppm is in opposite phase with water (initial protocol parameters, TE = 1.43 ms, bandwidth [BW] = 660 Hz/pixel) and (B) when in phase (TE = 1.03 ms, BW = 1930 Hz/pixel). These are averaged maps across subjects (n = 6) in the template space with 1 mm-isotropic resolution. Sagittal and coronal views are displayed in Supporting Information Figures S1 to S4. Red arrows point to the main differences appearing in the scalp (higher lipid content than in the brain tissue), mostly observed at −2.7, −3.3, and −3.5 ppm. The dotted-line red circle highlights a slight inhomogeneity of the contrast in the frontal lobe (with TE = 1.43 ms) and in the occipital lobe (with TE = 1.03 ms), which disappeared when using the parallel transmit (pTx) fat saturation.
Table 3: Summary of the main effects of the different fat suppression schemes on the z-spectrum.

| Offsets | ROIs | TE = 1.43 ms | CP fat sat + non-selective pTx excitation | pTx fat sat + non-selective pTx excitation | pTx water-excitation |
|-------|------|--------------|----------------------------------------|----------------------------------------|---------------------|
| 0 ppm | Upper WM and GM | In phase | +0.9% | +1.2% | +0.9% |
| -2.7 ppm | Upper WM and GM | In phase | +0.9% | +1.2% | +0.9% |
| -2.7 ppm | Upper WM and GM | In phase | +0.9% | +1.2% | +0.9% |
| -2.7 ppm | Upper WM and GM | In phase | +0.9% | +1.2% | +0.9% |
| -7.2 ppm | Upper WM and GM | In phase | +0.9% | +1.2% | +0.9% |
| -7.2 ppm | Upper WM and GM | In phase | +0.9% | +1.2% | +0.9% |
| -7.2 ppm | Upper WM and GM | In phase | +0.9% | +1.2% | +0.9% |
| -7.2 ppm | Upper WM and GM | In phase | +0.9% | +1.2% | +0.9% |
| -7.2 ppm | Upper WM and GM | In phase | +0.9% | +1.2% | +0.9% |

Note: Numbers indicate the relative difference with respect to the acquisition without fat suppression. Arrows were added as visual indication of the overall trend: ↑ for increase, ↓ for decrease, → for no difference (absolute difference below 1% were considered as no difference).

4 | DISCUSSION

In this preliminary study, the potential of dynamic pTx fat suppression pulse design was explored in the context of 7 T CEST MRI. The pulse design was based on a universal transmit k-space trajectory defined offline and a subject-specific RF pulse shape (amplitude and phase) optimization in the brain performed online, as previously proposed, without added acquisition time. Fat saturation and water-excitation pulses were considered. Based on Bloch simulations and in-vivo acquisitions, the fat suppression homogeneity was increased with pTx fat saturation, but the spectral selectivity was slightly degraded. Conversely, pTx water-excitation demonstrated a high spectral selectivity of water, but reduced the water FA homogeneity as compared to the non-selective pTx pulse. The largest average effects on in-vivo MTR asymmetry values were approximately −32% in the brain, with clear reductions in the z-spectrum dip observed in the offset region targeted by the pulses. These results are promising for the application of CEST in the body where fat and consequent artifacts are more substantial.

3.2.3 | Effects on Lorentzian model fitting

Figure 7 shows the average whole-brain maps obtained by fitting a 5-pool Lorentzian model to the z-spectrum after denoising. No striking differences were observed in the brain across the four fat suppression schemes. The main difference was seen for Amine (peak position −2.2 ppm) where higher values appeared in the posterior region of the brain when no fat suppression was applied (red dotted-line circle). These differences were quantified in more details by brain regions in Supporting Information Figure S7. Again, the use of pTx for fat saturation generally restored the same trend across the different brain regions (reduced peak amplitude), suggesting an improved homogeneity throughout the brain compared to fat saturation in CP mode. In particular, the largest (normalized) peak reductions with respect to the acquisition without fat suppression were observed with pTx fat saturation for Amine in the thalamus (−7.8%) and for rNOE in the frontal lobe (−7.2%). In general, the effects of the fat suppression schemes followed the same trend (with different amplitudes) across brain regions, except for pTx water-excitation, which mostly showed increased peak amplitudes for rNOE (e.g., +2.8% in the thalamus).

Again of the bias that fat can introduce in CEST contrasts quantification.
Magnetization Transfer Ratio (MTR) asymmetry difference with respect to the acquisition without fat suppression, quantified in different regions of the brain. (A): initial CEST protocol (TE = 1.43 ms, bandwidth [BW] = 660 Hz/px) where the water was in opposite phase with the fat peak at −3.3 ppm, targeted in the fat suppression pulse design; (B): modified CEST protocol (TE = 1.03 ms, BW = 1930 Hz/px) where the water was in phase with the fat peak at −3.3 ppm. The colored bars represent the mean value across healthy volunteers (n = 6) and the vertical black line represents the standard deviation. The calculated difference in percentage of the value obtained without fat suppression is: 100 × [MTR asym(fat suppressed acquisition) − MTR asym(acquisition without fat suppression)]/MTR asym(acquisition without fat suppression). The different brain regions can be visualized in Figure 3.
**FIGURE 7** Whole-brain CEST contrasts maps (transversal view) estimated with 5-pool Lorentzian model fitting for each fat suppression scheme: Amide Proton Transfer (APT), relayed-Nuclear Overhauser Effect (rNOE), semi-solid Magnetization Transfer pool (MT) and Amine. These are averaged maps across healthy volunteers \((n = 6)\) resulting from the acquisitions with the initial CEST protocol \((\text{TE} = 1.43 \text{ ms}, \text{BW} = 660 \text{ Hz/px})\) where water and the fat peak at \(-3.3 \text{ ppm} (\text{targeted in the fat suppression pulse design})\) where in opposite phase. Units are the fitted peak amplitude in percentage of the normalization signal \((M_0)\). Sagittal and coronal views are displayed in Supporting Information Figures S5 and S6.

### 4.1 Pulse design performance and hints for future work

The first results of this study demonstrate that better performances (FA homogeneity and accuracy) can be obtained with online subject-specific dynamic pTx fat saturation pulse design, as compared to standard CP fat saturation. In particular, the reduced pulse duration of the pTx fat saturation (25% shorter) provides the advantage of a reduced sensitivity to local \(B_0\) heterogeneities. Additionally, the short computational time (<40 s) enabled to perform the calculations during the anatomic (pTx) sequence acquisition, adding no extra-time to the protocol (because the \(B_0\) and \(B_1^+\) maps we already acquired). Those 3D pulses are not only interesting for whole-brain 7T CEST MRI, but can be easily transferred to any other 3D gradient-echo sequences.

The results suggest that dynamic pTx fat saturation would perform better than the current implementation of dynamic pTx water-excitation, in regards to the homogeneity and efficiency of fat suppression and the effects on in-vivo CEST metrics, although the water magnetization was affected, which could potentially translate into an SNR reduction. However, no particular effect on the z-spectrum amplitude or SNR reduction was observed in this study as compared to the acquisition with CP fat saturation (Figure 4).

The designed pTx fat saturation and water-excitation pulses increased the maximum local SED of the readout by 26% and 32% on average respectively, but this did not enforce stricter SAR constraints at the acquisition because of the long recovery time necessary for the CEST preparation. As shown in simulations (Figure 2), the allowed SED increase in the pulse design was crucial to improve performances, in particular for pTx fat saturation. Nevertheless, because of the improved FA homogeneity and accuracy, a lower target FA than 110° (e.g., 90°) could be used in future pulse design or for other applications to reduce the SED.

The spectral selectivity could still be improved. Indeed, a residual FA of 1.6° to 4.6° at the water frequency with pTx fat saturation and of 0.5° to 0.9° at the fat frequency with pTx water-excitation were obtained. Other transmit-k-space trajectories should be considered; in particular the stack-of-spirals with a denser sampling of the k-space center could be an interesting alternative for fat saturation pulses, which do not require high spatial frequencies. The spectral selectivity of the water-excitation pulse design would more benefit from a longer pulse...
duration (providing more degrees of freedom), although this would be at the cost of a longer readout, an increased sensitivity to $B_0$ variations and therefore, sub-optimal for CEST imaging where the CEST information included in the signal quickly decreases.\(^\text{16}\) In the authors’ opinion, the largest room for improvements stands at the universal trajectory determination, which was optimized for the FA homogeneity and accuracy but not for the spectral selectivity.

### 4.2 Effects on CEST metrics

This study demonstrates the complex and distorting effect of fat on the z-spectrum with in vivo data acquired at two different echo times and with the comparison of fat suppressed and non-suppressed acquisitions. In the absence of fat suppression, the z-spectrum values in the main fat region tend to increase when fat is not in phase with water, as demonstrated by Zhang et al.\(^\text{6}\) neglecting $T_2^*$ dephasing. Additionally, longer echo times might induce more dephasing of the fat signal. Therefore, in that case, the contribution of the direct saturation of fat on the z-spectrum dip in the corresponding spectral region might already be concealed, which would explain the mitigated effects of the fat suppression pulses when the targeted fat frequency was in opposed phase with water. Now when fat is in phase with water, the results obtained with pTx fat saturation show that, even in the brain WM and GM where a negligible lipid content is usually assumed, an artificial increase by 2.5% in average in the z-spectrum peak at $-3.5$ ppm can be obtained if the lipid signal is not suppressed at the acquisition. This artificial increase consequently reflects in the calculated $\text{MTR}_{\text{asym}}$ at $-3.5$ ppm ($r\text{NOE}$-weighted contrast) and symmetrically in the $\text{MTR}_{\text{asym}}$ at $+3.5$ ppm, often used as a surrogate for APT quantification, with potential overestimation in magnitude up to 28.4% of the value measured without fat suppression (Figure 6, in the parietal lobe) in this setup. This effect could be attributed to the suppression of lipid signal genuinely coming from the brain, but could also be due to subtle artifacts of the scalp fat signal aliasing into the brain that are hardly detectable. Note that the $\text{MTR}_{\text{asym}}$ map at $+3.5$ ppm, often referred as APT-weighted image, is the opposite of the $\text{MTR}_{\text{asym}}$ map at $-3.5$ ppm shown in Figure 5, and therefore, would have a reversed contrast, similar to the APT map in Figure 7 but with negative values because rNOE dominates at this low $B_1$ saturation level\(^\text{10}\).

Another demonstrated interest of effective and homogeneous fat suppression for CEST MRI is the increased amplitude of the water peak and of the z-spectrum in general. Even in the brain, the water peak amplitude was increased by up to 15% with pTx fat saturation, and almost by 50% in the scalp (Figure 4B). Although the comparison between tissues with different relaxation times is limited, in the absence of fat suppression, the water peak amplitude in the scalp was smaller than in the brain tissue (z-spectrum value of 0.45 at 0 ppm in the scalp vs. 0.05 in the brain WM and GM). When applying fat suppression (especially pTx fat saturation), this amplitude was increased (0.23 at 0 ppm). However, it did not reach the full amplitude measured in the brain tissue. This could potentially be due to residual fat not completely suppressed in the scalp (the optimization region of interest for the pulse design was the brain only), but it could also and most likely be explained by more substantial $B_0$ heterogeneities and/or imperfect CEST saturation in the scalp, resulting in a higher minimum z-spectrum value at 0 ppm even in the hypothetical case of a perfect fat suppression.

The effects observed on the estimated metabolites peak amplitudes from the 5-pool Lorentzian model fitting in the brain were only minor. The largest effects (~7%-8% reduction in peak amplitude) were again observed with pTx fat saturation in the thalamus for Amine as well as in the frontal lobe for rNOE (Supporting Information Figure S7), which is consistent with a reduction of the fat-induced bias in the rNOE estimation (“pseudo-rNOE”).\(^\text{5}\) The bias of the lipids signal on the z-spectrum in the brain might, therefore, probably be mitigated in the post-processing by the denoising and/or model fitting.

These pulses still remain interesting for an accurate quantification of rNOE and APT in the brain as well as in the case of fat aliasing artifacts from the scalp and strong $B_0$ heterogeneities in the vicinity of the sinuses or the eyes and ears at 7T. Furthermore, in this study, the implemented fat suppression schemes were applied to healthy volunteers only. Their benefits might be more significant in pathologic cases with increased fat content, such as in intracranial lipomas\(^\text{31,32}\) (mainly composed of adipose cells) or cerebral fat embolism.\(^\text{33}\)

Finally, as the current objective is to achieve a fast whole-brain CEST protocol, the resolution was limited compared to slab-selective protocols, which can presently reach a resolution up to $1.8 \times 1.8 \text{mm}^2$ in-plane.\(^\text{23}\) Partial volume effects, for example between WM and GM or between GM and cerebrospinal fluid, might therefore have partially mitigated the effects of lipid suppression.

### 4.3 Perspective for application in the body

In this preliminary study, the proposed dynamic pTx fat suppression pulse designs were applied to the brain where lipids are much less abundant than in other body regions. More significant benefits are therefore expected for the
application of CEST in the body. As a matter of fact, the suppression of the lipid signal was the main source of concern in a recent application of 7T CEST in the breast. The lipid artifacts in CEST MRI of the lumber spine, arising from B₀ heterogeneities, were also recently described with the conclusion that large B₀ heterogeneities in the body were the limiting factor for fat suppression using water-selective binomial pulses. Abdominal and musculoskeletal applications are additional regions of interest where fat is a major impediment, for instance in joints imaging where partial volume effects are unavoidable.

A method very similar to the one used is this study had been used for the design of fat saturation pulses for 3T MRI of the knee, with the optimization of the pulse shape based on the B₀ and B₁⁺ maps and given SPINS and spokes transmit trajectories. However, the calculations were performed using the small-tip-angle approximation and a subsequent linear scaling of the pulse amplitude to 90°. Although several parameters were determined empirically and proof-of-concept was showed in only one healthy volunteer, interesting performances were obtained as compared to Shinnar-Le Roux spectrally selective fat saturation pulses, with a reduced pulse duration, suggesting that the small-tip-angle approximation errors might be negligible for fat saturation in such organs. Comparison with this optimization method is therefore warranted.

In organs smaller than the head, lower B₁⁺ heterogeneities are expected. Therefore, a denser sampling of the transmit-k-space center might be more beneficial to increase the spectral selectivity without compromising the FA homogeneity. Spirals and stack-of-spirals, but also SPINS trajectories could be good candidate for fat saturation pulses in this case. For short water-selective excitation, the SPINS trajectory seems to remain a good choice.

The current barrier to use pTx pulses in those organs is the low availability of multi-transmit coils. Nevertheless, online subject-specific dynamic pulse optimization based on B₀ and B₁⁺ maps can still be performed with single-transmit coils to mitigate B₀ heterogeneities at 7T despite the limited degrees of freedom. Ongoing work focuses on the translation of this implementation to the application of CEST MRI in the knee at 7T.

5 CONCLUSION

This preliminary study demonstrated that an improved homogeneity in the fat suppression can be obtained at 7T using online individually optimized dynamic pTx pulses. The best performances were obtained with pTx fat saturation based on a kₚ-points trajectory. The highest effects on CEST contrasts in the brain were observed when lipids were in phase with water, suggesting an overestimation of the MTR asymmetry magnitude at ±3.5 ppm up to 28.4% in average when no fat suppression is applied. A higher bias and therefore more benefits of the technique are expected in the body where fat is more substantial and B₀ heterogeneities more severe than in the head.

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CONFLICT OF INTEREST

The co-author David Grodzki is an employee of Siemens Healthcare. The first author, Simon Lévy, and the second author, Jürgen Herrler, are now also employees of Siemens Healthcare (since the 15th of June 2022 and the 1st of April 2022, respectively), however most of this work was performed before they became Siemens Healthcare employees, as described by their affiliation.

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REFERENCES
1. Jones KM, Pollard AC, Pagel MD. Clinical applications of chemical exchange saturation transfer (CEST) MRI: clinical applications of CEST MRI. J Magn Reson Imaging. 2018;47:11-27.
2. Jones CK, Schlosser MJ, van Zijl PCM, Pomper MG, Golay X, Zhou J. Amide proton transfer imaging of human brain tumors at 3T. Magn Reson Med. 2006;56:585-592.
3. McVicar N, Li AX, Gonçalves DF, et al. Quantitative tissue Ph measurement during cerebral ischemia using amine and amide concentration-independent detection (AACID) with MRI. J Cereb Blood Flow Metab. 2014;34:690-698.
4. Zhou J, Heo HY, Knutsson L, van Zijl PCM, Jiang S. APT-weighted MRI: techniques, current neuro applications, and challenging issues: APTw MRI for neuro applications. J Magn Reson Imaging. 2019;50:347-364.
5. Lu J, Zhou J, Cai C, Cai S, Chen Z. Observation of true and pseudo NOE signals using CEST-MRI and CEST-MRS sequences with and without lipid suppression: observation of true and pseudo NOE signals. Magn Reson Med. 2015;73:1615-1622.
6. Zhang S, Keupp J, Wang X, et al. Z-spectrum appearance and interpretation in the presence of fat: influence of acquisition parameters. Magn Reson Med. 2018;79:2731-2737.
1. Zimmermann F, Korzowski A, Breitling J, et al. A novel normalization for amide proton transfer CEST MRI to correct for fat signal-induced artifacts: application to human breast cancer imaging. Magn Reson Med. 2020;83:920-934.

2. Hamilton G, Yokoo T, Bydder M, et al. In vivo characterization of THE liver fat 1H MR spectrum: IN VIVO CHARACTERIZATION OF THE LIVER FAT 1H SPECTRUM. NMR Biomed. 2011;24:784-790.

3. Zhao Y, Zu Z, Wang Z, et al. Effectiveness of fat suppression using a water-selective binomial-pulse excitation in chemical exchange saturation transfer (CEST) magnetic resonance imaging. Magn Reson Mater Phys Biol Med. 2020;33:809-818.

4. Padormo F, Beqiri A, Hajnal JV, Malik SJ. Parallel transmission for ultrahigh-field imaging: parallel transmission for ultrahigh-field imaging. NMR Biomed. 2016;29:1145-1161.

5. Meyer CH, Pauly JM, Macovski and A, Nishimura DG. Simultaneous spatial and spectral selective excitation. Magn Reson Med. 1990;15:287-304.

6. Zhao F, Nielsen JF, Noll DC. Four dimensional spectral-spatial fat saturation pulse design. Magn Reson Med. 2014;72:1637-1647.

7. Gras V, Vignaud A, Amadon A, Le Bihan D, Boulant N. Universal pulses: a new concept for calibration-free parallel transmission: calibration-free parallel transmission. Magn Reson Med. 2017;77:635-643.

8. Liebert A, Zaiss M, Gumbrecht R, et al. Multiple interleaved mode saturation (MIMOSA) for B1 + inhomogeneity mitigation in chemical exchange saturation transfer. Magn Reson Med. 2019;82:693-705.

9. Liebert A, Tkotz K, Herrer J, et al. Whole-brain quantitative CEST MRI at 7T using parallel transmission methods and correction. Magn Reson Med. 2021;86:346-362.

10. Zaiss M, Ehses P, Scheffler K. Snapshot-CEST: optimizing spiral-parallel acquisition for fast and robust 3D CEST MRI at 9.4 T. NMR Biomed. 2018;31:e3879.

11. Herrler J, Liebig P, Gumbrecht R, et al. Fast online-customized (FOCUS) parallel transmission pulses: a combination of universal pulses and individual optimization. Magn Reson Med. 2021;85:3140-3153.

12. Cloos MA, Boulant N, Luong M, et al. KT-points: short three-dimensional tailored RF pulses for flip-angle homogenization over an extended volume. Magn Reson Med. 2012;67:72-80.

13. Ugray Z, Lasdon L, Plummer J, Glover F, Kelly J, Marti R. Scatter search and local NLP solvers: a multistart framework for global optimization. Inf J Comput. 2007;19:328-340.

14. Wächter A, Biegler L.T. On the implementation of an interior-point filter line-search algorithm for large-scale nonlinear programming. Math Program. 2006;106:25-57.

15. Majewski K. Simultaneous optimization of radio frequency and gradient waveforms with exact hessians and slew rate constraints applied to kT -points excitation. J Magn Reson. 2021;326:106941.

16. Ashburner J, Friston KJ. Unified segmentation. Neuroimage. 2005;26:839-851.

17. Mennecke A, Khakzar KM, German A, et al. 7 tricks for 7 T CEST: improving reproducibility of multi-pool evaluation provides insights into effects of age and early stage Parkinson's disease. NMR Biomed. 2022;e4717.

18. Zaiss M, Schmitt B, Bachert K. Relaxation-compensated CEST-MRI of the human brain at 7T: unbiased insight into NOE and amide signal changes in human glioblastoma. Neuroimage. 2015;112:180-188.

19. Jones CK, Polders D, Hua J, et al. In vivo three-dimensional whole-brain pulsed steady-state chemical exchange saturation transfer at 7T. Magn Reson Med. 2012;67:1579-1589.

20. Sood S, Gupta R. Susceptibility artifacts in ruptured intracranial Derrm cysts: a poorly understood but important phenomenon. Neuroradiol J. 2014;27:677-684.

21. Yildiz H, Hakyemez B, Koroglu M, Yesildag A, Baykal B. Intracranial lipomas: importance of localization. Neuroradiology. 2006;48(1):1-7.

22. Yeap P, Kanodia AK, Main G, Yong A. Role of susceptibility-weighted imaging in demonstration of cerebral fat embolism. BMJ Case Rep. 2015;2015:bcr2014207581.

**SUPPORTING INFORMATION**

Additional supporting information may be found in the online version of the article at the publisher’s website.

**Figure S1:** Sagittal view of the whole-brain MTR asymmetry maps at $-2.7$, $-3.3$, $-3.5$, and $-4.7$ ppm obtained with each fat suppression scheme (averaged maps across subjects in the template space with 1mm-isotropic resolution) and with TE $= 1.43$ ms (resulting in a relation of opposite phase between water and the targeted fat peak at $-3.3$ ppm).

**Figure S2:** Coronal view of the whole-brain MTR asymmetry maps at $-2.7$, $-3.3$, $-3.5$, and $-4.7$ ppm (averaged maps across subjects in the template space with 1mm-isotropic resolution) and with TE $= 1.43$ ms (resulting in a relation of opposite phase between water and the fat peak at $-3.3$ ppm targeted in the pulse design).

**Figure S3:** Sagittal view of the whole-brain MTR asymmetry maps at $-2.7$, $-3.3$, $-3.5$, and $-4.7$ ppm obtained with each fat suppression scheme (averaged maps across subjects in the template space with 1mm-isotropic resolution)
and with TE = 1.03 ms (resulting in an in-phase relation between water and the fat peak at −3.3 ppm, targeted in the fat suppression pulse design)

**Figure S4:** Coronal view of the whole-brain MTR asymmetry maps at −2.7, −3.3, −3.5, and −4.7 ppm obtained with each fat scheme (averaged maps across subjects in the template space with 1 mm-isotropic resolution) and with TE = 1.03 ms (resulting in an in-phase relation between water and the fat peak at −3.3 ppm, targeted in the fat suppression pulse design)

**Figure S5:** Sagittal view of the whole-brain CEST contrasts maps obtained with each fat suppression scheme (averaged maps across subjects in the template space with 1 mm-isotropic resolution) and with the initial CEST protocol (TE = 1.43 ms, BW = 660 Hz/pixel)

**Figure S6:** Coronal view of the whole-brain CEST contrasts maps obtained with each fat suppression scheme (averaged maps across subjects in the template space with 1 mm-isotropic resolution) and with the initial CEST protocol (TE = 1.43 ms, BW = 660 Hz/pixel)

**Figure S7:** Peak amplitude difference obtained with each fat suppression scheme (with respect to the acquisition without fat suppression) for the main CEST contrasts in different brain regions

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