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B_1^+ Inhomogeneity Mitigation in CEST Using Parallel Transmission

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Purpose: In order to benefit from the increased spectral bandwidth at ultrahigh field (UHF), the use of parallel transmission (pTx) to mitigate flip-angle inhomogeneity in chemical exchange saturation transfer (CEST) imaging is investigated.

Theory and Methods: A pTx basis pulse is homogenised by magnitude least-squares (MLS) optimization and expanded to form a frequency-selective saturation pulse for CEST. The pTx saturation pulse was simulated with a three-pool Bloch-McConnell equation to evaluate the impact of pTx on CEST contrast. In vivo CEST imaging performance (7 T) of the pTx saturation pulse and the standard Gaussian saturation in circularly polarized mode were compared. Two-spokes pTx homogeneous excitation was used in all in vivo experiments to ensure fair comparison of the two saturation pulses. Magnetization transfer ratio and inverse Z-spectrum analyses were used as metrics in evaluating the data from 3 healthy volunteers.

Results: Bloch-McConnell simulations showed that side bands of the pTx saturation pulse at ± 20 ppm did not affect any CEST contrast. Improved homogeneity in contrasts and relaxation-compensated CEST metrics were observed in our in vivo data when the pTx saturation pulse was used.

Conclusion: A pTx-based pulsed CEST presaturation scheme is proposed and validated by simulations and 7T in vivo imaging. **Magn Reson Med 78:2216–2225, 2017. © 2017 International Society for Magnetic Resonance in Medicine.**

Key words: chemical exchange saturation transfer; pulsed CEST; ultra-high-field MRI; parallel transmission; RF inhomogeneity; RF pulse design

INTRODUCTION

Chemical exchange saturation transfer (CEST) imaging is an MR technique that enables the indirect detection of metabolites using the water MR signal (1). CEST is based on the phenomenon of saturation transfer from a solute pool, in part, comprising metabolites, to the water pool resulting in a modified contrast depending on the metabolite concentration and the exchange rate between the two pools (2). Repeating the measurements at different saturation frequencies enables the acquisition of the so-called Z-spectrum, where the contrast of different metabolites is encoded. Furthermore, depending on the saturation pulse amplitude (B_1^+), the method is sensitive to different exchange rates. Consequently, the contrast for a certain metabolite is B_1^+ dependent and can be maximized. This is a promising MRI technique with many applications, such as measurement of glycogen (GlycoCEST) (3), glutamate (GluCEST) (4), and glucose (GlucoseCEST) (5). It can also be used to measure amino acids by amide proton transfer (APT), which has applications in brain tumors and stroke attributed to the pH dependence of the contrast (6–8). A more-detailed description of CEST theory and applications can be found in previous works (9,10).

CEST imaging benefits from higher static magnetic fields attributed to the increased spectral dispersion. However, for in vivo application in humans at ultrahigh field (UHF), (e.g., 7 T), practical limitations arise attributed to the higher specific absorption rate (SAR) and B_1^+ inhomogeneity: SAR constrains the range of possible B_1^+ that can be applied and consequently exchange rate saturation efficiency, whereas the B_1^+ inhomogeneity introduces spatial variation in the CEST contrast.

The limitations imposed by B_1^+ in the context of CEST imaging have been addressed by several methods, such as magnetization transfer ratio asymmetry magnetisation transfer ratio (MTR_{asym}) correction using a calibration factor in phantoms (11), double-frequency irradiation (12), or Lorentzian line fits using multiple B_1^+ amplitudes (13) for postprocessing of highly resolved Z-spectra. Nonetheless, the majority of those methods rely on additional measurements to calculate calibration or interpolation factors.

Parallel transmission (pTx) has been used to mitigate flip-angle inhomogeneity in MRI at UHF, for example, by means of slice-selective spokes excitations (14). By driving each transmit channel independently with time-varying amplitude and phase modulations (15), radiofrequency (RF) pulses can be optimized to achieve a homogeneous flip-angle distribution. pTx has been used in CEST at 3T to overcome the RF duty cycle constraints imposed by the RF amplifiers in clinical scanners (16).

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The interleaved transmit approach allows continuous wave saturation to be mimicked in brain (16) and kidney (17) CEST imaging at 3T. Both of these studies did not exploit the possibilities of using pTx to achieve homogeneous saturation and excitation, and, to the best of our knowledge, this has not been explored for CEST at UHF.

The goal of this work is to develop and explore the potential of using pTx to achieve homogeneous saturation and excitation for pulsed-CEST human in vivo imaging on a 7T human MR scanner.

THEORY

pTx Pulse Design

The flip-angle homogenization of RF pulses can be achieved by solving a regularized magnitude least square (MLS) (18) problem under small tip-angle approximation (19)

$$\mathbf{b} = \arg \min_{\mathbf{b}} \{ \|\mathbf{A}\mathbf{b}\| - \|\mathbf{m}\|_2^2 + \lambda \|\mathbf{b}\|_2^2 \}, \quad [1]$$

where $\mathbf{b}$ is a column vector containing the complex RF scaling factors for each of the transmit channels for all the RF time points, $\mathbf{A}$ is the system matrix formed according to the spatial domain method (20) containing information about off-resonance, excitation k-space trajectory, and transmit sensitivity, $\mathbf{m}$ is a column vector representing the transverse magnetization target in the volume-of-interest (VOI), and λ is the Tikhonov regularization parameter as a means to regularize the global RF power. This problem can be solved efficiently with the multishift version of the conjugate gradients for least squares algorithm, in which the solutions of a set of λ can be obtained simultaneously in a single iteration (21). In order to avoid solutions with B_1^+ voids (22), which could occur at local minima during the optimization, a region-growing algorithm was utilized in the process in which $\mathbf{b}$ is first solved for a small subregion at the center of the VOI before being fed into the next iteration on a bigger subregion as the initial value (23).

Slice-Selective Excitation

For 2D imaging, a class of pTx pulses called “spokes” has shown promising homogenization capability at 7T (14). Spokes pulses typically consist of slice-selective pulses that are fully adjustable in both phase and amplitude per transmit channel, played out once or multiple times with interleaved x- and y-gradient blips to provide an effective spatial phase variation of the transverse magnetisation as an extra degree of freedom. The periodic spatial phase variation generated by the gradient blips can be viewed as a point on the k_x - k_y plane in the excitation k-space. Static RF shimming can be considered as the special case of one spoke at the k-space center. The required phases and amplitudes for the subpulses can be found using the MLS optimization described above.

CEST Saturation Pulse

A desirable saturation pulse for CEST should have the properties of frequency selectivity as well as spatially homogenized saturation. These two properties can be

achieved in a two-step method. First, a spatially and spectrally nonselective basis pulse with spatially homogenized low flip-angle with short pulse duration is designed. A type of k-space trajectory called spiral nonselective (SPINS) has been demonstrated to be effective in homogenizing excitations (24) and is a suitable candidate for designing such a basis pulse. In Cartesian coordinates, the k-space trajectory under a SPINS pulses can be defined as

$$\begin{aligned} k_x(t) &= k_r(t) \sin(ut) \cos(vt), \\ k_y(t) &= k_r(t) \cos(ut), \\ k_z(t) &= k_r(t) \sin(ut) \sin(vt), \end{aligned} \quad [2]$$

where $k_r(t) = k_{\max} (1 + \exp[\alpha(\frac{t}{T} - \beta)])^{-1}$, $k_{\max}$ is the maximum distance of the trajectory from the k-space center, T is the pulse duration, and α , β , u , and v define the rate at which the 3D spiral is traveled. k_y and k_z in Equation 2 are swapped from the original definition in Malik et al (24) to make the trajectory travel mostly within the k_x - k_y plane. With the defined k-space trajectory, the basis pulse is designed by the MLS optimization in the same fashion as the spokes pulse for excitation to yield a spatially homogeneous flip-angle.

In the second step, the desired saturation pulse for CEST is designed by adding frequency selectivity to the flip-angle homogenized basis pulse. As in the case of single-channel transmission, the frequency profile and bandwidth of an RF pulse are determined by the amplitude modulation (i.e., the waveform) and its length, respectively, in time domain. Typically, a Gaussian waveform is used because of its frequency selective capabilities in pulsed-CEST sequences (25).

The frequency selectivity of a long-duration Gaussian pulse and the spatial homogeneity of the basis pulse can be combined by repeating the short-duration basis pulse for the same period of time as the Gaussian pulse and imposing the profile of the Gaussian pulse onto the resulting composite pulse. Mathematically, in time domain, this is equivalent to a convolution of the basis pulse with a series of delta functions with a period equal to the duration of the basis pulse itself and a multiplication of the resulting composite pulse with a Gaussian amplitude modulation. By the convolution theorem, the frequency response of the resulting pulse is the frequency profile of the Gaussian modulation convolved with a series of delta functions with a period equal to the inverse of the duration of the basis pulse and multiplied with the frequency profile of the basis pulse. In other words, the selective frequency profile of a long-duration Gaussian pulse is preserved in the final pulse, but with its profile repeated in the frequency domain at a rate determined by the inverse of the basis pulse duration. This rate of repetition in turn determines the separation of the side bands of the pTx pulse, hence the usable range of its off-resonance saturation. In typical CEST experiments, where chemical shifts are often in a range of ± 5.0 ppm, the repeated Gaussian profiles at frequencies over ± 10 ppm away should not affect the CEST contrasts, and only the central peak can be considered as the sole provider of the saturation exchange effect. Given

FIG. 1. Schematic of the two-step pTx saturation pulse formation in the time and frequency domains. The bottom row is the same pulse plotted in a frequency range of ± 30 ppm.

that the basis pulse is designed to have a very short duration, the repeated profiles in frequency domain can be readily designed up to 20 ppm apart at 7T. Also, because of the short duration of the basis pulse, and hence its high bandwidth, its broad frequency profile only slightly modulates the frequency profile of the central peak. Figure 1 summarizes the two-step pTx saturation pulse design process. Hereafter in this article, the pTx and standard saturation pulses are denoted as pTxCEST and circularly polarized (CP)-mode CEST, respectively.

METHODS

MR Measurements

MR acquisitions were performed on a 7T MR scanner (MAGNETOM; Siemens Medical Solutions, Erlangen, Germany) with a whole-body gradient set (SC72; maximum amplitude, 70 mT/m; maximum slew rate, 200 T/m/s) and an eight-channel transmit/32-channel receive head coil (Nova Medical, Wilmington, MA, USA) in pTx mode (step 2.3, 1 kW per channel). All experiments were carried out in the vendor-provided “protected mode” in which the total and per-channel RF power limits were set by taking the worst-case local SAR derived from the transmit coil’s electromagnetic (EM) simulations into account to ensure SAR-safe operations at a safety margin of approximately factor of 2.5. In order to provide an indication that the desired imaging protocols were under the local SAR limits (10 seconds average of 20 W/kg, 6 minutes average of 10 W/kg), local SAR predictions were made during the pulse design according to the formalism in Graesslin et al (26). The SAR matrices were calculated from EM simulation results provided by the coil

manufacturer (adult male [Hugo] EM model; field values and tissue properties were exported to MATLAB [The MathWorks, Inc., Natick, MA, USA] in 2-mm isotropic resolution with $28 \times 28 \times 28 \text{ cm}^3$ coverage). A safety margin of factor 2 was applied to the local SAR calculations following the recommendations found in Hoffmann et al (27). To speed up the local SAR prediction, the list of SAR matrices was compressed using a vendor-provided program, which works according to the virtual observation points (VOPs) method (28). An overestimate limit of 7% was chosen as the compression parameter because it provided a good balance between the compression ratio (164 VOPs from 890,074 SAR matrices) and the overestimation. Three healthy volunteers participated in this study. After a complete description of the study, written informed consent was obtained before scanning.

RF Pulse Calculations and Bloch Simulations

RF pulse optimisations were carried out in MATLAB (The MathWorks, Inc., Natick, MA, USA) on a separate multicore computer connected to the MR scanner. The target slice positions for the imaging slice or the VOI for the saturation pulse were exported directly from the imaging protocol on the scanner. The B_0 and B_1^+ maps required for the RF pulse optimization were obtained from a dual-echo 3D gradient echo (GRE) and a transmit phase-encoded (29), T_2 and T_2^* compensated version of DREAM (30), respectively. The flip-angle spatial distribution of all the excitation and saturation pulses used in the imaging experiments were mapped with the pre-saturation turbo-flash (PreSat-TFL) sequence (31). Details of the B_0 and B_1^+ mapping protocols can be found in Tse et al (32). The pulse optimizations were restricted to only brain regions (i.e., VOI) by using FSL-

BET (33) brain masks generated from the magnitude images of the B_0 and B_1^+ maps.

Excitation flip-angle has been shown to influence CEST contrasts in small animal imaging at 9.4T (34). To minimize the influence of the excitation flip-angle inhomogeneity on the comparison of the pTxCEST and CP-mode CEST saturation pulses, two-spoke pulses were used in all CEST experiments to provide homogenized excitations (see Supporting Fig. S1). The two spokes were located at $\{[6.52, 0], [0, 0]\} \text{ m}^{-1}$ in the k_x - k_y plane of the excitation k -space. A fly-back slice-selective gradient was used to avoid the slice-dependent phase difference between the positive and negative gradient lobes attributed to a RF-gradient delay. The *sinc* subpulse used in the experiment had a bandwidth time product of 2.7 and a duration of 2.39 ms, with a subpulse peak-to-peak separation of 3.3 ms. Further details of the excitation pulse design can be found in Tse et al (35).

Two different saturation pulses were compared in the CEST imaging experiments. The first saturation pulse (CP-mode CEST) was a standard *sinc*-modulated Gaussian pulse of duration 18.7 ms (corresponding to a full width at half maximum [FWHM] of 0.5 ppm) played out in CP mode; the second saturation pulse (pTxCEST) was the pTx-enabled saturation pulse described in the Theory section, which also has the same 18.7-ms duration and 0.5-ppm FWHM as the CP-mode CEST pulse. The amplitude of the pTxCEST pulse was modulated with the same Gaussian profile as the CP-mode CEST pulse. The k -space trajectory of the basis pulse for pTxCEST was set according to Equation 2 with $\alpha=10$, $\beta=0.5$, $u=8\pi \text{ rad ms}^{-1}$, $v=2\pi \text{ rad ms}^{-1}$, and $T=0.07 \text{ ms}$. Including a gradient ramp from the k -space center, the overall duration of the k -space trajectory of the basis pulse was 0.11 ms. The voltage amplitudes of the two saturation pulses were calibrated with the flip-angle maps acquired with the PreSat-TFL sequence (31). The calibration ensured that both pulses achieved the same mean flip-angle, that is, the same effective B_1^+ power (Eqs. 1 and 2 in Zu et al (36)), in the VOI at 0.0 ppm. To demonstrate the frequency response of the SPINS basis pulse and the two saturation pulses, Bloch simulations were performed for a frequency range of $\pm 25 \text{ ppm}$ using an in vivo B_0 and B_1^+ data set.

Bloch-McConnell Simulations of CEST Contrasts

In the frequency domain, the pTxCEST saturation pulse exhibits side bands separated by 20 ppm (Fig. 1). In order to investigate the effects of these side bands on CEST contrasts, a three-pool (amide, direction saturation, and semisolid macromolecular magnetization transfer [MT]) simulation was performed in MATLAB. The MT pool was modelled as a Super-Lorentzian curve where the effects of the different bands were summed. Simulation parameters can be found in Jones et al (37). The spatial distribution of the RF pulse amplitude was calculated from the transmit sensitivity maps of the individual channels and the waveforms applied to the transmit channels. The RF voltage amplitudes of the CP-mode CEST and pTxCEST pulses were calibrated against each

other using the mean flip-angle within the VOI. Both pulses were simulated using a train of 120 pulses with a duty cycle of 50% and 18-ms total pulse duration at effective B_1^+ powers of 0.3, 0.6, and $1.0 \mu\text{T}$. The MTR_{asym} (38) and the inverse amide proton transfer MTR_{Rex} (δ_{amide}) (39,40) using the multi-Lorentzian fitting approach (13,41) were evaluated from simulation results for both saturation pulses (8,40). In addition, to evaluate the contribution of the MT pool from the side bands in the CEST contrast, simulations with and without the MT pool were performed.

CEST Imaging Experiment

To ensure an artefact-free imaging comparison of the two saturation pulses, a 2D GRE sequence (single-shot centric acquisition for CEST; echo time = 4.39 ms; repetition time = 9.2 ms; matrix size = 80×80 ; flip-angle = 10° ; slice-thickness = 6.5 mm) was chosen as the CEST imaging sequence. The CEST presaturation was a train of 120 saturation pulses (the CP-mode CEST or pTxCEST pulses described above) with a duty cycle of 50%. For both types of saturation pulses, Z-spectra were sampled from -300 to 300 ppm at 69 unevenly distributed points. Total acquisition time was 6 minutes. An effective B_1^+ power (36) of $0.6 \mu\text{T}$ was used to evaluate both of the saturation pulses. For this protocol, the maximum 10 seconds and 6 minutes averaged local SAR for the two-spoke excitation pulse were estimated to be 0.02 W/kg , and for the CP-mode CEST and pTxCEST saturation pulse trains were 2.15 W/kg and 3.45 W/kg , respectively. For B_0 correction, water saturation shift reference (WASSR) data were also acquired using the same GRE imaging readout and a saturation frequency range of -1.5 to 1.5 ppm , divided in 60 steps of 0.05 ppm (42).

CEST Contrast and Data Analysis

The CEST images were first B_0 -corrected based on the WASSR method (42) and then normalized using the image acquired at 300 ppm . Two approaches were used to obtain the CEST contrast and evaluate the effect of the saturation pulses: MTR_{asym} (38) and the inverse Z-spectrum analysis (39,40) with the multi-Lorentzian fitting method (13,41). MTR_{asym} is a widely used metric for CEST evaluation, and it is given by the difference of the signals at the amide frequency (3.5 ppm) and at the opposite side of the water frequency (-3.5 ppm) (8)

$$\text{MTR}_{\text{asym}}(3.5 \text{ ppm}) = Z(-3.5 \text{ ppm}) - Z(3.5 \text{ ppm}). \quad [3]$$

The inverse Z-spectrum ($1/Z$) method is based on the equivalence between the spin lock and CEST experiments (40). APT-weighted and nuclear Overhauser effect (NOE)-weighted images can be obtained from this approach. The metric MTR_{Rex} is defined as

$$\text{MTR}_{\text{Rex}}(\delta_i) = \frac{1}{Z_{\text{lab}}(\delta_i)} - \frac{1}{Z_{\text{ref}}(\delta_i)}, \quad [4]$$

where $\delta_i = 3.5 \text{ ppm}$ for amide MTR_{Rex} , $\delta_i = -3.5 \text{ ppm}$ for NOE MTR_{Rex} , the reference $1/Z_{\text{ref}}$ is the sum of all fitted Lorentzian functions except the labeled species, and

FIG. 2. Bloch simulations of the saturation pulses. (a) Normalized flip-angle spatial distribution of the pTx basis pulse, the CP-mode CEST, and the pTxCEST saturation pulses at a range of off-resonance frequencies. (b–d) Flip-angle averaged over the VOI in a frequency range of ± 25 ppm for the basis pTx pulse (pulse amplitude, 28.0 V), the CP-mode CEST (8.2 V), and the pTxCEST saturation pulse (14.0 V). Inserts in (c) and (d) show the normalized flip-angle spatial distribution integrated over the central peak (± 0.5 ppm).

$1/Z_{lab}$ is the fitted Lorentzian to the labeled specie. T_1 relaxation was not considered in the analysis because it is independent of B_1^+ (13).

RESULTS

Bloch Simulations of Saturation Pulses

The results of Bloch simulations of the two saturation pulses, CP-mode CEST and pTxCEST, as well as the pTx basis pulse are presented in Figure 2. Figure 2a shows the spatial distribution of the normalized flip-angle of these pulses at various off-resonance frequencies,

whereas Figure 2b–d plots the flip-angle averaged over the VOI in the frequency range of ± 25 ppm. The low flip-angle basis pulse has a broadband spectrum with a FWHM of 20 ppm. The basis pulse demonstrates a spatially homogenized flip with normalized root mean square errors (NRMSE) of 0.041. Both the CP-mode CEST and pTxCEST saturation pulses show a narrow bandwidth (FWHM, 0.5 ppm). Small side bands at ± 20 ppm can be seen in the pTxCEST saturation. The inserts in Figure 2c,d are the spatial distribution of the normalized flip-angle integrated over the central peak (± 0.5 ppm), which show a more spatially homogeneous saturation

FIG. 3. Top row: Bloch-McConnell simulations of Z-spectra for both CP-mode CEST and pTxCEST saturations at different effective B_1^+ powers. Bottom row: CEST contrasts evaluated in metrics MTR_{asym} and MTR_{Rex} over the effective B_1^+ amplitude range.

FIG. 4. PreSat-TFL flip-angle maps of the excitations (left) and saturations (center), as well as B_0 off-resonance maps (right) acquired in 3 healthy volunteers. Slice location corresponds to the CEST imaging slice.

provided by the pTxCEST (NRMSE 0.042) in comparison to the CP-mode CEST pulse (NRMSE 0.122).

Bloch-McConnell Simulations of CEST Contrasts

Figure 3 shows the simulation results for different levels of saturation power for both CP-mode CEST and pTxCEST pulse trains. In the Z-spectra, additional peaks can be seen in the pTxCEST saturation at ± 20 ppm because of their side bands (Fig. 2d). In the ± 5.0 -ppm range, both saturation schemes give identical Z-spectra. The MT contribution from the side bands was inferior to 0.005%, 0.02%, and 0.06% in the amplitude of the CEST peak at 3.5 ppm for 0.3, 0.6, and 1.0 μT , respectively. The plots of CEST metrics, MTR_{asym} and $\text{MTR}_{\text{rex}}(\delta_{\text{amide}})$ against the effective B_1^+ amplitude also show no observable difference between the two saturation pulses. This implies that both CP-mode CEST and pTxCEST saturation pulses result in the same APT contrast when the same effective B_1^+ amplitude is delivered to the same VOI.

CEST Imaging Experiment

The B_0 off-resonance maps, the PreSat-TFL flip-angle maps of the CP-mode and two-spokes excitations, as well as the CP-mode CEST and pTxCEST saturations at the position of the CEST imaging slice from 3 healthy volunteers are presented in Figure 4. Flip-angle maps of

the excitation pulses demonstrate the homogeneous excitations provided by the two-spoke pulse, which successfully eliminates the central brightening that is observed in the CP-mode excitation. The average excitation NRMSE across the 3 volunteers reduced from 0.11 (CP-mode) to 0.05 (two-spokes). The flip-angle maps of CP-mode CEST and pTxCEST saturation pulses at 0.00 ppm are presented here in effective B_1^+ power. It can be seen that the CP-mode CEST saturation pulse only reached the desired 0.6 μT effective B_1^+ power in the central brightening spot, whereas the pTxCEST pulse managed to homogeneously deliver the desired saturation power across the entire brain region within the imaging slice. In both CP-mode CEST and pTxCEST saturations, some regions of the brain were not shown to be saturated in all 3 volunteers. This is because the B_0 off-resonance in those regions was larger than the 0.5 ppm bandwidth of both saturation pulses (for reference, see the B_0 maps shown in Fig. 4).

Figure 5 shows the Z-spectra from both CP-mode CEST and pTxCEST saturations. The Z-spectra from two different locations in white matter, as shown in the brain image in Figure 5, are presented here. As predicted by Bloch-McConnell simulations (Fig. 3), reductions in signal can be seen at ± 20 ppm for the pTxCEST saturation attributed to its side bands. Within the typical frequency range for evaluating MTR_{asym} (i.e., ± 5 ppm), no effect of

FIG. 5. Z-spectra obtained with CP-mode CEST and pTxCEST saturation pulses, at the two different white matter locations indicated in the brain image on the left.

FIG. 6. CEST parametric maps from the CP-mode CEST and pTxCEST saturation schemes. White arrows highlight the areas where pTxCEST showed improvements over CP-mode CEST saturation. Inhomogeneous CP-mode saturation led to overestimations in $MTR_{\text{rex}}(\delta_{\text{NOE}})$ and $MTR_{\text{rex}}(\delta_{\text{APT}})$ in the center of the brain. In MTR_{asym} , improvements in gray matter contrast can be seen in the pTxCEST saturation.

the side bands can be observed. Despite the fact that both spectra are taken from white matter tissue, the spectra in CP-mode CEST saturation display noticeable differences. This is caused by the B_1^+ inhomogeneity in the CP-mode saturation, which led to different effective B_1^+ saturation powers in the two voxels.

CEST parametric maps are presented in Figure 6. Undesired contrast variations, for example, attributed to B_1^+ inhomogeneity rather than tissue difference, can be observed in the maps acquired with the CP-mode CEST saturation, but not in those with the pTxCEST saturation. This is more evident in both the NOE and amide MTR_{rex} than MTR_{asym} , because the inverse of a Z-spectrum is a more-sensitive metric. In the MTR_{asym} maps, a small improvement in contrast can be seen in gray matter from the pTxCEST saturation. These observations agree well with the flip-angle distributions shown in Figure 4.

DISCUSSION

This work presents a method to design a parallel-transmit saturation pulse for CEST to mitigate against undesired contrast variations caused by the B_1^+ inhomogeneity at UHF. The homogeneous pTxCEST saturation pulse was evaluated by simulations as well as in vivo human brain imaging at 7T.

The CEST imaging sequence utilises a small flip-angle slice-selective pulse. Using MLS optimization, a two-spoke pulse was successfully designed to homogenize the excitation, resulting in a 50% reduction in NRMSE in comparison with CP-mode excitation. This improvement is comparable to previously published results (14,35). The

previously observed effect of excitation flip-angle on CEST contrasts (34) was not clearly observed in our preliminary study (see Supporting Figs. S1 and S2). Nonetheless, homogeneous excitations were used in our imaging experiments to ensure that the comparison between the two saturation pulses was free from any potential influence caused by an inhomogeneous excitation pattern.

The pTxCEST saturation was designed in two steps which combine the benefits of the spatially homogenized flip from the pTx basis pulse with the frequency selectivity of a Gaussian pulse, a typical choice for saturation in CEST experiments. While the pTx saturation preserves the bandwidth of the Gaussian envelope, it creates side bands as shown in Figures 1 to 3. This leaves a usable range of ± 10 ppm, which exceeds the typical saturation range in CEST experiments using MTR_{asym} and hence poses no practical constraints. In this study, the SPINS (24) k-space trajectory was chosen over kT-points (43) because of its efficiency in covering excitation k-space which allows a shorter basis pulse duration and hence a wider separation of side bands. Furthermore, no influence in CEST contrasts was found in the Bloch-McConnell simulations (Fig. 3). Even in densely sampled Z-spectra, the side-band frequencies can be easily avoided given that they are determined by the length of the basis pulse. Nonetheless, the side bands should be taken into account in CEST analyses, such as the three-point (39) and the sum of Lorentzian functions methods (7,13,41,44,45), to avoid erroneously fitting the pTx side bands as an extra CEST contrast contribution. The pTxCEST side bands can introduce extra contributions from the macromolecular pool to the CEST peak, which

is power dependent. Nevertheless, such contribution is smaller than 0.06% at 3.5 ppm for 1.0 μ T, and no effect was found in the CEST metrics. Moreover, the MT pool only has limited contribution in the range of saturation powers used in this work (46).

Both Bloch simulations (Fig. 2) and in vivo mapping (Fig. 4) show that pTxCEST provided spatially more homogeneous saturation than CP mode. Previous works have shown that the excitation and saturation inhomogeneity in CP mode at 7T caused higher CEST contrast in the center of the brain, where the bright spot of the CP mode is (13,47). Our simulations indicated a reduction by 60% in the saturation NRMSE for pTxCEST. This improvement should translate into spatially homogenized saturation and hence more-reliable CEST contrast. This is indicated by the reduced variability in the white matter Z-spectra between ± 5 ppm (Fig. 5) when pTxCEST saturation was used. Also, the same improvements can be seen in the CEST parametric maps (Fig. 6).

B_1^+ inhomogeneity needs to be taken care of for quantitative imaging at UHF, including CEST. Solutions to the problem of CEST contrast variation caused by B_1^+ inhomogeneity include the use of adiabatic pulses (48) and a simultaneous analysis of B_1^+ from acquired CEST data (49). Corrections can be applied in postprocessing and/or analysis when extra CEST measurements can be acquired at several levels of saturation B_1^+ amplitude (13,45). This is the natural choice for Omega plot analysis (50) which by default requires data from several saturation powers, which could take up to tens of minutes. For clinical scans, attributable to limits in scan time and patient comfort, it is often the case that the CEST image is only acquired with a single saturation power (51,52). In these cases, pTx offers an attractive solution to the problem of undesired contrast variations caused by B_1^+ inhomogeneity. Typically, the B_1^+ maps measurement, which is required for the pTx pulse calculation, takes around 1 minute and the pulse calculation itself takes further 1 to 2 minutes, hence already providing a saving in time compared with the postprocessing method. Further time saving can potentially be achieved by using precalibrated pTx pulses (53). These will help to translate clinical applications of CEST from 3 to 7T and field strengths beyond (54,55) to fully benefit from the increased signal-to-noise ratio and spectral bandwidth.

Because of the increased SAR at UHF, only relatively low B_1^+ amplitudes (0.6 μ T) were used in our experiments. This is also common in other human CEST studies performed in UHF (6,44) and it is sufficient to demonstrate the potential of pTx in CEST imaging. Local SAR hotspots are concerns in pTx applications (26,27). In this study, we used a vendor-provided SAR monitor mode which has a conservative limit, which in turn restricted the maximum B_1^+ amplitude available. Local and global SAR information in VOP-compressed SAR matrices can be used as constraints during a least-squares (LS) pulse optimization (56–58). Compared with the MLS approach, which was used here, the constrained LS optimization has been shown to perform worse in terms of homogenization and both global and local SAR (18,56). Local SAR monitoring using VOP-compressed SAR matrices could potentially be used to

relax the restriction on the maximum B_1^+ amplitude. However, given that one of the main applications of CEST is tumor imaging, we decided that a conservative SAR limit would be more suitable to demonstrate the potential benefits of pTx for CEST. This is because the water content and conductivity in tumor tissues differ from normal brain tissues (59,60). SAR matrices derived from EM-models with healthy brains may not be valid for all subjects.

2D GRE was used to showcase the homogeneous pTxCEST saturation because it is a robust imaging sequence that does not (unlike fast imaging sequences) suffer from many imaging artefacts that might have obscured the comparison of pTxCEST and regular CP-mode CEST. Of course, pTxCEST is a general, non-volume-selective saturation pulse and therefore it can be readily applied in other fast 3D CEST imaging techniques, such as echo planar imaging (61), gradient and spin echo (38), or in a steady-state pulsed approach (37). pTxCEST also lends itself as a homogenized saturation pulse in other UHF applications, such as water or fat saturations in single-voxel spectroscopy and chemical shift imaging.

CONCLUSION

A homogenized saturation pTx pulse, termed pTxCEST, was proposed and evaluated for the use in CEST imaging in healthy volunteers at 7T. The homogenized saturation pulse significantly reduced the undesired CEST contrast variation attributed to B_1^+ inhomogeneity.

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article

Fig. S1. Flip-angle maps of CP-mode (left) and the two-spoke (right) excitation pulses.

Fig. S2. $MTR_{\text{Rex}}(\delta_{\text{NOE}})$ parametric maps obtained from pTxCEST saturation with CP-mode and two-spoke excitations. Only minimal differences can be seen in these two images, suggesting that the main contribution for undesired CEST contrast variations is the saturation pulse.