INTRODUCTION

CEST MRI uses the transfer of magnetization of solutes to water by means of proton exchange. By saturating a relatively rare proton species that is in chemical exchange with the abundant water protons, a relatively small effect can be amplified.\(^1,2\) This effect allows enhanced detection of metabolites\(^3\)–\(^8\) and proteins in vivo.\(^9\)–\(^11\) The phenomenon can be understood by a mechanistic model: the magnetization of the solute proton is reduced by saturation, the saturated solute proton is transferred to the unsaturated water proton pool, and the magnetization of the water pool decreases until a new
equilibrium is reached. Unfortunately, this mechanistic model is not able to clearly explain transient CEST effects, the interplay with direct water saturation, or semisolid magnetization transfer contributions.

CEST can also be understood as a relaxation phenomenon\(^9,12\) by considering the relaxation during radio-frequency irradiation, also known as the relaxation in the rotating frame \(T_{1p}\) and \(T_{2p}\).\(^13\) This theoretical insight not only allows us to understand the transient behavior elegantly as \(T_{1p}\)-decay toward the new steady-state of \(T_{1p}/T_1\), but also allows for incorporation of influences of CEST and magnetization transfer contributions into the \(T_{1p}\)- and thus the CEST-Equation\(^14\). The comparison with \(T_{1p}\)-measurements by the spin-lock technique (SL) also gives insight into how to reduce direct water saturation. In a typical CEST experiment, a long pulse is used to “saturate” a magnetization vector (Figure 1A). For

![Figure 1](image)

**Figure 1** Amplitude (\(\omega_1(t)\)) and frequency (\(\omega_{RF} - \omega_0\)) modulation and the corresponding trajectory of the Magnetization vector for a cw CEST (A), conventional SL (B), hyperbolic secant nonmatching SL (C), and a hyperbolic secant matching SL (D) saturation scheme. Blue lines show the on-resonant trajectory, red lines the trajectory at 2 ppm. The tip of the magnetization vector at the end of the pulse is marked with a colored dot in the graph. A, The on-resonant saturation is just a rotation around the y'-axis. Applied off-resonant, the magnetization rotates around the effective field \(B_{eff} = (B_1, 0, \Delta \omega/\gamma)\). B, The classical SL shows the ideal result at optimal conditions. The rotations are suppressed in both cases. However, \(B_0\) and \(B_1\) inhomogeneity can strongly disturb this behavior. C, While the on-resonant case yields robust SL (the \(B_{eff}\) direction stays stationary during the whole pulse), the off-resonant case shows strong oscillations similar to A. D, The power of the locking pulse was matched to the power of the adiabatic tilting pulse. This pulse yields controlled magnetization both on- and off-resonant, as in the ideal SL (B), but is robust against \(B_0\) and \(B_1\) inhomogeneity.
a continuous wave (cw) experiment, this means that the CEST magnetization at the irradiation frequency rotates around the y-axis and decays (blue line, Figure 1A); at the same time, the nearby water magnetization vector follows the off-resonant rotations around \( \vec{B}_{\text{eff}} \) (red line, Figure 1A). SL pulses inherently suppress these oscillations and restore transverse magnetization after the locking period (Figure 1B).

Instead of the on-resonant flip-angle behavior in a CEST experiment (Figure 1A), typically resulting in strong saturation and oscillation artifacts, SL allows insight into the on-resonant \( T_{1p} \)-decay, which has itself a unique chemical-exchange weighting. At each irradiation frequency offset, the ideal SL experiment would only show \( T_{1p} (\Delta \omega) \)-decay along the longitudinal axis of the rotating frame, while all components in the transverse plane of the rotating frame, namely \( T_{2p} \) decay and any rotations, would be suppressed. An experiment with such ideal SL pulses would yield a \( T_{1p} \)-dominated Z-spectrum with low influence from direct water saturation, and strong chemical exchange weighting in the magnetization of each saturation frequency offset. Thus, such a Z-spectrum would be beneficial for the acquisition and evaluation of CEST effects in vivo.

As shown by Jin and Kim, chemical exchange-weighting in SL experiments greatly benefits from higher field strengths. Thus, in this work we aim to investigate Z-spectrum acquisition using SL pulses for in vivo applications at 9.4 T. While conventional on- and off-resonant SL experiments can be directly performed at a spectrometer, on a whole-body-system SL approaches need to overcome artifacts due to \( B_0 \) and \( B_1 \) inhomogeneity. One approach to do so is using adiabatically prepared SL pulses, which was shown to yield \( R_1p \)-maps without oscillation imaging artifacts for on-resonant SL at 7 T. However, these pulses cannot be used for off-resonant SL, because the amplitude mismatch between the adiabatic preparation pulse and the rectangular locking pulse leads to an erratic behavior of the magnetization (red line, Figure 1C).

In addition, even in the on-resonant case, at 9.4 T the same approach was not able to avoid oscillation artifacts due to the amplifier-limited maximum pulse amplitude. Matching the amplitude of the adiabatic tipping and the locking pulse improves the stability of the magnetization vector trajectory, because it overcomes this erratic behavior of the magnetization (Figure 1D). However, designing such a pulse is complex, regarding the limitation of the \( B_1 \) amplitude of the adiabatic pulse by the typically low power locking pulse.

The aim of this study was to design such an adjusted adiabatic SL pulse with matching amplitude, for on- and off-resonant use, to enable a \( T_{1p} \)-dominated Z-spectrum acquisition. Design criteria were robustness against \( B_1 \) and \( B_0 \) inhomogeneity as well as a usability at low \( B_1 \) power deposition (~5 \( \mu \)T). To achieve that, Bloch simulations were used to find an optimized pulse shape which resulted in the most similar magnetization behavior to an ideal SL pulse. The optimized SL pulse was then implemented and evaluated using phantom and in vivo MRI measurements at ultra-high-field (UHF).

2 | METHODS

2.1 | Theoretical description

An SL experiment uses a rectangular locking pulse, defined by an amplitude \( \omega_0 \) and a frequency offset \( \Delta \omega \), which is applied in between two tipping pulses (Figure 1C,D). The first tipping pulse brings the magnetization vector to the effective frame, which is tilted by the angle \( \theta = \text{atan}(\omega_0/\Delta \omega) \) with respect to the z-axis (see Figure 1B-D). For the on-resonant case, the flip angle of these pulses would be \( \theta = 90^\circ \) and locking would occur along the transverse plane. The second tipping pulse, following the rectangular locking pulse, is used to tilt the magnetization back in z direction. When adiabatic pulses are used as tipping pulses, the on-resonant SL pulse is prepared by an adiabatic half passage pulse (AHP). The AHP can be described as a time-dependent vector \( \vec{B}_{\text{eff}}(t) \).

\[
\vec{B}_{\text{eff}} (t) = \begin{pmatrix} B_z (t) \\ 0 \\ B_x (t) \end{pmatrix} = \begin{pmatrix} B_1(t) \\ 0 \\ \frac{1}{\gamma} (\Delta \omega_p (t)) \end{pmatrix}
\]

where \( B_1(t) \) is the amplitude and \( \Delta \omega_p (t) \) is the frequency offset of the pulse, defined as the difference between the carrier frequency of the pulse \( \omega_\text{RF}(t) \) and the Larmor frequency \( \omega_0 (\Delta \omega_p (t) = \omega_\text{RF}(t) - \omega_0) \). A commonly used AHP pulse is the hyperbolic secant (HS) pulse described by the following formulas:

\[
B_1 (t) = B_{1,\max} \cdot \text{sech} \left( \frac{\pi \cdot \Delta f}{\mu} \cdot (t - t_{\text{adia}}) \right)
\]

\[
\Delta \omega_p (t) = \pi \cdot \Delta f \cdot \tanh \left( \frac{\pi \cdot \Delta f}{\mu} \cdot (t - t_{\text{adia}}) \right) + \Delta \omega.
\]

Here, \( B_{1,\max} \) is the maximal amplitude, \( \Delta f \) is the bandwidth, \( t_{\text{adia}} \) the duration of the AHP pulse, \( \mu \) is a dimensionless parameter controlling the FWHM of the HS function and \( \Delta \omega \) is a constant frequency offset. The amplitude and frequency modulation of such a pulse shape for \( B_{1,\max} = 20 \mu \)T, \( \Delta f = 1200 \) Hz, \( \tau_p \approx 8 \) ms, \( \mu = 6 \), and \( \Delta \omega = 0 \) Hz is shown in Figure 2A. The long plateau phase of the frequency modulation in combination with the late and steep increase of the amplitude modulation, leads to a fast rotation of \( \vec{B}_{\text{eff}} \) after approximately 5 ms and can cause violations of the adiabatic
condition for low power pulses. Increasing the FWHM of the hyperbolic secant function, namely \( \mu \), results not only in a more gradual amplitude increase, but also in an amplitude offset at \( t_0 = 0 \) ms (dotted line, Figure 2A). This offset causes an erratic behavior of the magnetization, because the initial magnetization is not aligned with \( \vec{B}_{eff}(t_0) \).

The adjusted HS pulse proposed here is depicted in Figure 2B. To overcome the amplitude offset, we introduced a windowed amplitude modulation (blue line, Figure 2B). For the frequency modulation, we chose an exponential function, to avoid the long plateau phase of the hyperbolic tangent function (Equation 3). This adjusted pulse shape is herein after referred to as HSExp. The windowing is defined by its length \( t_{\text{window}} \), resulting in a time-dependent function \( H(t) \):

\[
H(t) = \begin{cases} 
0.42 - 0.5 \cdot \cos \left( \frac{\pi \cdot \Delta f \cdot (t - t_p)}{t_{\text{window}}} \right) + 0.08 \cdot \cos \left( \frac{2 \pi \cdot t}{t_{\text{window}}} \right) & \text{if } t \leq t_{\text{window}}, \\
1 & \text{if } t > t_{\text{window}}.
\end{cases}
\] (4)

The complete description of the adjusted pulse shape then reads as:

\[
B_1(t) = B_{1,max} \cdot \operatorname{sech} \left( \frac{\pi \cdot \Delta f}{\mu} \cdot (t - t_p) \right) \cdot H(t)
\] (5)

\[
\Delta \omega_p(t) = \pi \cdot \Delta f \cdot \exp \left( -\frac{t}{t_p} \cdot \operatorname{ef} \right) - \exp \left( -\operatorname{ef} \right) + \Delta \omega.
\] (6)

The dimensionless parameter \( \operatorname{ef} \) was introduced to control the steepness of the exponential curve. During the locking period with pulse duration \( T_{SL} \), the effective field \( \vec{B}_{eff} = (B_1, 0, \Delta \omega/\gamma) \) is constant and the magnetization decays along the vector \( \vec{B}_{eff} \), which is known as the \( R_1^\phi \)‐decay (\( R_1^\phi = 1/T_1^\phi \)) described by:

\[
M_z(T_{SL}) = (M_i - M_{ss}) \cdot \exp \left( -T_{SL} \cdot R_1^\phi \right) + M_{ss}
\] (7)

where \( M_i \) is the initial z‐magnetization before the pulse, \( R_1^\phi = 1/T_1^\phi \) is the tissue‐dependent longitudinal relaxation rate in the rotating frame, and \( M_{ss} \) is the steady‐state magnetization given by:

\[
M_{ss}(\theta) = M_0 \cdot \frac{R_{1w} \cdot \cos(\theta)}{R_{1\rho}^\phi}.
\] (8)

For on‐resonant experiments, \( M_{ss} = 0 \). \( R_{1\rho}^\phi \) depends on \( \omega_1 \), \( \Delta \omega \), the relaxation rates, and an exchange term \( R_{ex}^\phi \) and can be written as:

\[
R_{1\rho}(\theta) = R_{1w} \cdot \cos^2(\theta) + R_{2w} \cdot \sin^2(\theta) + R_{ex}^\phi = R_{eff}(\theta) + R_{ex}^\phi.
\] (9)
The quantity \( R'_{ex} \) is the exchange-dependent relaxation rate in the rotating frame and can contain exchange or semi-solid magnetization transfer related contributions. The exchange dependent relaxation term \( R'_{ex} \) is defined by \( \omega_\Delta, \Delta \omega \), the concentration \( f_b \), the exchange rate \( k_b \), the chemical shift with respect to water \( \delta\omega_b \), as well as the longitudinal \( R_{1b} \) and transversal relaxation rate \( R_{2b} \) of the solute pool b. Assuming the exchange rate to be much larger than relaxation rates of pool b \( (k_b >> R_{1b}, R_{2b}) \), \( R_{1b} \) and \( R_{2b} \) can be neglected and \( R'_{ex} \) can be described as:

\[
R'_{ex} (\Delta\omega_b) = f_b k_b \frac{\delta\omega_b}{\omega_\Delta^2 + \Delta\omega^2} \frac{\omega_\Delta^2}{\omega_\Delta^2 + \Delta\omega^2} + f_b k_b \sin^2 \theta \frac{\omega_\Delta^2}{\omega_\Delta^2 + \Delta\omega^2}.
\]  

Equation (10) is valid for on- and off-resonant SL, but can be simplified in the on-resonant case to \(^{13}\):

\[
R'_{ex} (\Delta\omega = 0) = f_b k_b \frac{\delta\omega_b^2}{\omega_\Delta^2 + \delta\omega_b^2 + k_b^2}.
\]  

According to Equation (12) the exchange term is also present in the case of an FID \( (\omega_\Delta = 0) \), meaning that the observed \( R_2 \), namely \( R_{2,obs} \), is a mixture of the actual \( R_2 \) of the water pool and the \( R_{ex} \) of the exchanging pools, also known as the Swift-Connick relation.\(^ {16} \)

\[
R_{2,obs} = R_{2w} + f_b k_b \frac{\delta\omega_b^2}{\omega_\Delta^2 + \delta\omega_b^2 + k_b^2}.
\]  

In the presence of a locking pulse this behavior turns from an FID into an on-resonant \( R_{1p} \) decay:

\[
R_{1p} = R_{2w} + f_b k_b \frac{\delta\omega_b^2}{\omega_\Delta^2 + \delta\omega_b^2 + k_b^2}.
\]  

Thus, \( R_{1p} \) and the observed relaxation rates \( R_{1,obs} \) and \( R_{2,obs} \) are functions of the pure water relaxation \( R_{1w} \) and \( R_{2w} \) as well as of coupled pools. Pure \( R_{1w} \) and \( R_{2w} \) are unknown, as we can only measure \( R_{1,obs} \) and \( R_{2,obs} \). A direct quantification of \( R_{ex} \) by subtracting \( R_{eff} \) from the measured \( R_{1p} \) is, therefore, not possible. To make a coarse estimation, we can use \( R_{1,obs} \) and \( R_{2,obs} \) instead of \( R_{1w} \) and \( R_{2w} \) as they are accessible, and Equation (9) can be used to calculate a pure theoretical \( R_{eff} \) that we call \( R_{eff,obs} \) here for comparison:

\[
R_{eff,obs} = R_{1obs} \cdot \cos^2 (\theta) + R_{2obs} \cdot \sin^2 (\theta).
\]  

The decay of \( R_{eff,obs} \) over different frequency offsets is shown in Figure 3C (black dotted line). In this simulation, \( R_{eff,obs} \) is greater than \( R_{1p} \) for \( \Delta\omega \leq 0.15 \) ppm but smaller for \( \Delta\omega > 0.15 \) ppm.

Equation (7) is only valid for a constant locking pulse but can be extended for an ideal adiabatic pulse by integration of the actual pulse shape using the step-wise approximation, which we refer to as \( Z_{R_{1p}} \), the \( R_{1p} \)-dominated \( Z \)-spectrum:

\[
Z_{R_{1p},\Delta\omega} \left( \Delta\omega, \omega_1 \right) = \left( Z_{ref,n} \left( \Delta\omega, \omega_1 \right) - M_{ss,n} \left( \Delta\omega, \omega_1 \right) \right) \cdot \exp \left( -R_{1p,s} \left( \Delta\omega, \omega_1 \right) \cdot \Delta t \right) + M_{ss,n} \left( \Delta\omega, \omega_1 \right) \cdot \exp \left( -R_{1p,s} \left( \Delta\omega, \omega_1 \right) \cdot \Delta t \right).
\]  

When using the eigenvalue approach as presented by Trott and Palmer\(^ {13} \) and Zaiss and Bachert,\(^ {12} \) this equation describes an ideal adiabatic SL as only one eigenvalue (namely \( R_{1p} \)) is incorporated, with no oscillation eigenvalues and no \( T_2 \). Thus, \( Z_{R_{1p}} \) forms a reference solution for an adiabatic SL pulse with perfect locking, yielding an \( R_{1p} \)-dominated \( Z \)-spectrum. For a real adiabatic SL pulse, all eigenvalues must be taken into account by integrating the full Bloch equations for shaped pulses.

### 2.2 Simulation

To find optimal pulse parameters for robust application in the presence of \( B_1 \) and \( B_0 \) inhomogeneity, a full Bloch simulation of the adiabatic pulses was performed sample-wise, using 200 samples per AHP pulse, as played out at the scanner. The pulse response was then calculated for 500 evenly distributed frequency offsets in the range of \( \pm 3 \) ppm. This simulation was performed for 18 different combinations of \( B_0 \) and \( B_1 \) inhomogeneity based on the typical \( B_1 \)- and \( B_0 \)-maps in vivo at the used 9.4 T system. Six \( B_1 \) values ranging from 65% to 130% of nominal power (3.25-6.5 µT) and 3 \( \Delta B_0 \) values of 0, 30, and 60 Hz were incorporated into the simulations. The resulting 18 \( Z \)-spectra were simulated for different parameter combinations of the proposed adjusted pulse shape (HSExp), namely \( 1 \leq \mu \leq 80, 0.5 \text{ ms} \leq \tau_{\text{window}} \leq 3.5 \text{ ms}, \) and \( 1000 \text{ Hz} \leq \Delta f \leq 9000 \text{ Hz}, \) using the full Bloch
equations yielding a stack $Z_{\text{full}}$, and using the ideal single-eigenvalue Bloch equations (Equation 17) yielding a stack $Z_{R1p}$ as a reference. The cost function to be minimized was then the sum of squares of the difference ($SSD$) of $Z_{R1}$ and the full Bloch solution $Z_{\text{full}}$:

\[
SSD = \text{sum}((Z_{\text{full}} - Z_{R1p})^2).
\] (18)

Fixed parameters were $t_{\text{adia}} = 8\text{ ms}$ and $B_1 = 5\mu T$ as proposed by Schuenke et al for the HS pulses.\textsuperscript{5} The $ef$ factor as described in Equation (6) was set to 3.5, based on previous simulations.

2.3 | MRI measurements

MR imaging was performed on a 9.4 T whole-body system (Siemens Healthcare, Erlangen, Germany) under approval by the local ethics committee on five healthy volunteers who provided informed consent. Two different custom-built head coils were used for signal transmission/reception, either with 16 transmit/31 receive channels\textsuperscript{17} or 18 transmit/32 receive channels.\textsuperscript{18} The RF and gradient spoiled gradient-echo snapshot readout\textsuperscript{19} of approximately 3 s was used with a base matrix of 144 with 80% FOV in the first phase-encoding direction and 18 slices. The flip angle was $6^\circ$, TE = 2.13 ms, TR = 4.2, BW = 560 Hz/px, resolution $1.5 \times 1.5 \times 2\text{ mm}^3$. Parallel imaging acceleration factor 3 was applied in the phase encoding direction with GRAPPA reconstruction\textsuperscript{20} performed offline. Before postprocessing, all in vivo images were corrected for motion, using the AFNI’s 3Dvolreg function.\textsuperscript{21}

2.4 | $T_{1p}$-Decay measurements

An on- and off-resonant $T_{1p}$ measurement was acquired in a healthy volunteer. On-resonant the HSExp pulse was compared with the HS pulse presented in Schuenke et al\textsuperscript{6} because the typical $B_1$ distribution of 16/31 coil yields an effective $B_1$ amplitude of approximately 75% of the nominal value, the locking amplitude was set to 6.5 $\mu T$ to achieve a
mean value of approximately 5 µT in the FOV. The maximum amplitude of the HS pulse was limited to 20 µT by amplifier restrictions, resulting in an effective value of approximately 15 µT.

The off-resonant measurement was acquired at Δω = ±1 ppm and the HSExp pulse was compared with a single Gaussian pulse with amplitude matched to the cw power equivalent (cwpe) and pulse duration matched to TSL. For T1p measurements, images were acquired at 19 different locking times from 0.5 to 50 ms, with denser sampling between 0.5 and 10 ms.

2.5 | Z-Spectrum measurements

2.5.1 | Phantom measurements

In a phantom MRI measurement at room temperature, the HSExp pulse was compared with a clinical CEST protocol with Gaussian saturation pulses. The phantom consisted of seven cylindrical tubes filled with solutions of different glucose concentrations in a PBS buffer with a pH of 7.0. Glucose concentrations of the solutions in the tubes were 2 × 100 mM, 2 × 50 mM, 2 × 25 mM and 1 × pure PBS.

Using the HSExp pulse, the saturation phase consisted of two pulses with TSL = 100 ms with 75% duty cycle. Both rectangular locking pulses were surrounded by an AHP and an inverse AHP pulse. The Gaussian saturation scheme consisted of two 100 ms pulses with 75% duty cycle. Z-Spectrum measurement consisted of 48 evenly distributed offsets between ±3 ppm. For both pulses this Z-spectrum was acquired in a healthy volunteer for different B1 amplitudes, defined as the mean amplitude between ±3 ppm. Recovery time between the measurements consisted of 48 evenly distributed offsets between ±3 ppm. Both of these measurements, images were acquired at 19 different locking times from 0.5 to 50 ms, with denser sampling between 0.5 and 10 ms.

2.5.2 | In vivo measurements

In vivo, Z-spectra were acquired with two different protocols. First, a single HSExp pulse using B1,max = 6.5 µT was compared with an amplitude-matched Gaussian pulse (B1,cwpe = 6.5 µT) in the saturation block. The pulse duration t_p of the Gaussian pulse was matched to TSL of the HSExp pulse (50 ms). To reveal potential high frequency oscillation in the spectrum, 91 saturated images were acquired with dense frequency sampling at evenly distributed frequency offsets between ±3 ppm. Recovery time between the measurements of subsequent offsets was 5 s.

In a second experiment, the hypothesis of less direct water saturation by the HSExp pulse was tested by comparing Z-spectra acquired with saturation from a train of HSExp SL pulses to spectra acquired with saturation using a train of rectangular pulses of the same amplitude. The saturation phase consisted of six rectangular saturation pulses with t_p = 100 ms and 50% duty cycle; identical parameters were chosen for the HSExp with TSL = tp. A similar saturation scheme, but with a duration of 7.9 s was used by Rerich et al22 for a creatine weighted CEST contrast. Due to specific absorption rate (SAR) limitations, this long saturation phase was not possible for our measurement. The Z-spectrum measurement consisted of 35 evenly distributed offsets between ±4 ppm. Both of these protocols were repeated for B1 amplitudes, 2 µT, 2.5 µT, and 3 µT, providing glutamate or creatine weighted CEST imaging preparation.

2.5.3 | Postprocessing

All Z-spectrum data were corrected for B0 inhomogeneity using the WASABI approach3 and evaluated using MTR asym.

\[
MTR_{asym} = \frac{M_{sat}(-\Delta \omega) - M_{sat}(\Delta \omega)}{M_0}
\]  

Here, M_{sat} is the saturated image at a specific frequency and M_0 the fully relaxed normalization scan (saturated at Δω = −300 ppm).

3 | RESULTS

3.1 | Simulation

For the boundary conditions of B1,adia = B1,lock = 5 µT and t_{adia} = 8 ms, the HSExp parameters resulting in the minimal SSD = 0.573 were μ = 45, t_{window} = 2.5 ms, and Δf = 3000 Hz. For all parameters, the SSD from the HSExp shape was notably lower than with a matching amplitude HS pulse (Figure 2D, E). The deviation from the optimal Z_R1p curve for both pulses is shown in Figure 2C. Figure 4 shows the trajectory of the magnetization vector during the optimized HSExp pulse. The angle between the magnetization and \vec{B}_{eff} during the locking pulse remains small both on- and off-resonant, which suppresses oscillation artifacts. In the presence of B0 and B1 inhomogeneity, the magnetization vector still stays close to \vec{B}_{eff}.

3.2 | On-resonant T1p measurements

The optimized HSExp pulse was implemented in a CEST sequence for 9.4 T and SL prepared images of the brain were acquired in a healthy volunteer for different TSL times. Figure 5 shows the measured T1p decay for a single voxel in gray matter (GM) and white matter (WM), that could be fitted with a mono-exponential curve, to determine T1p (Equation (7)). The resulting fit values from the HSExp pulse experiment, namely T1p = 45.4 ms for the GM and T1p = 49.2 ms for the WM voxel, were then used in a Bloch simulation, to verify the measured values. In both simulation and measurement,
FIGURE 4  A–C, The trajectory of the magnetization vector during the HSExp SL pulse, with the on-resonant case without field inhomogeneity (A), the trajectory at 1 ppm without field inhomogeneity (B), and the on-resonant SL pulse in the presence of B₀ inhomogeneity (C). D, The different phases of the SL pulse.

FIGURE 5  Performance of T₁ρ measurements with the on-resonant SL pulses nonmatched HS (A,B) and matched HSExp (C,D) in a single-voxel of GM (A,C) and WM (B,D). The field inhomogeneities in the GM and WM voxel were 0.11 ppm/0.04 ppm for B_{01} and 60.5%/67.4% for B₁, respectively, and led to the visible oscillations in the decay curves of the HS pulse (red markers in A,B). Oscillations are similar in magnitude when simulations include inhomogeneities (blue lines in A,B). In comparison, the HSExp pulse generates smaller oscillations in both experimental (red markers in C,D) and simulated data (blue lines in C,D), even though the applied tipping power of 6.5 µT was less than a third of the power applied by the HS pulse. The black lines show the simulated decay curves for the nominal B₁ = 5 µT. Here the oscillation almost disappears using the HSExp pulse, but not using the nonmatched HS pulse.
the HSExp pulse resulted in smaller oscillations than the HS pulse. Moreover, when increasing the B1 power in the simulation, the oscillation almost disappeared for the HSExp pulse. This effect was not observed for the HS pulse.

The exponential fit was performed voxel-wise to generate an $R_{1p}$-map. The on-resonant $R_{1p}$-maps of the center slice using both pulses (HSExp and unmatched HS) are shown in Figure 6. The HS pulse results in visible artifacts in areas of low B1, while the HSExp pulse generates a flat image. The HSExp $R_{1p}$-map is without oscillations, and only reflects the $B_1$-dependency of $R_{1p}$ (Equation 9). Thus, in the on-resonant case, the amplitude matched HSExp pulse with $B_{1,\text{adia,max}} \approx 5 \mu T$ performed more robustly than the HS pulse with $B_{1,\text{adia,max}} \approx 15 \mu T$. In regions of interest (ROIs) drawn in WM and GM (Figure 6F), the measured $R_{1p}$ was $21.52 \pm 0.64$ Hz and $18.72 \pm 0.76$ Hz, respectively.

### 3.3 Off-resonant $T_{1p}$ measurements

To test the HSExp pulse off-resonant, simple Gaussian saturation pulses were used for comparison, as the amplitude-matched HS pulse performs very poorly at low power (Figure 2D). The off-resonant $R_{1p}$-map generated by the HSExp SL preparation showed no oscillation artifacts at 1 ppm (Figure 7E). ROI values for $R_{1p}$ using the HSExp pulse were $10.68 \pm 0.48$ Hz for GM and $11.36 \pm 0.37$ Hz for WM in the center slice.

The $R_{1p}$ values mapped using the Gaussian saturation pulse were $9.99 \pm 0.29$ Hz for GM and $10.02 \pm 0.37$ Hz for WM. However, several points had to be excluded to generate a proper fit (Figure 7C), because the very short Gaussian pulses violate the adiabatic condition. The $B_{\text{eff}}$ of the Gaussian pulse is always moving, so the measured $T_{1p}$ value is averaged between the decay along the different $B_{\text{eff}}$ directions, which makes quantification more difficult. This result again demonstrates the ability of the HSExp pulse to avoid oscillation artifacts, even for very short locking times.

### 3.4 Z-spectrum measurements

Having shown good performance in on- and off-resonant $T_{1p}$ decays, the HSExp pulse can now be applied for $T_{1p}$-dominated Z-spectrum acquisition.

#### 3.4.1 Comparison with Gaussian pulses in a phantom

Figure 8D,H,L show CEST contrast at 1.3 ppm generated by HSExp pulse. At a locking power $\geq 2 \mu T$, the HSExp pulse resulted in smaller oscillations than the HS pulse. Moreover, when increasing the B1 power in the simulation, the oscillation almost disappeared for the HSExp pulse. This effect was not observed for the HS pulse.
saturation pulse showed a higher asymmetry than the Gaussian pulse (Figure 8M). The MTR asym value increases with glucose concentration and saturation power for both pulses (Figure 8A,E,I). In the on-resonant case, the HSExp pulse generated images without visible oscillation artifacts, as long as the applied B1 power is ≥3µT (Figure 8B,F,J). The off-resonant approach did not generate visible oscillation artifacts at any applied power (Figure 8C,G,K).

3.4.2 | Comparison in vivo for a single pulse (SL regime, tsat ≈ 50 ms)

Z-spectra acquired with a single HSExp pulse showed a continuous curve along the entire frequency axis (Figure 9A), even in regions with a very low B1. Within the ±1 ppm range the Gaussian pulse changes its behavior toward an on-resonant flip angle rotation of the water magnetization, leading to very strong direct water saturation, while the HSExp pulse only exhibits the on-resonant T1ρ−decay. This behavior can be seen in the Z-spectrum as well as in the asymmetry analysis. The MTR asym images confirm the robustness of the HSExp pulse close to Δω = 0 (Figure 9F,G), where less oscillation artifacts are visible compared with the Gaussian pulse.

3.4.3 | Comparison in vivo for a pulse train (CEST regime, tsat > 1 s)

In a last experiment, a whole pulse train of six HSExp SL pulses or six rectangular pulses was used for saturation with tsat =1.1 s. Again, the SL-Z-spectra were more narrow compared with the conventional Z-spectra (Figure 10A). The frequency offset at 2 ppm was reported to correlate with creatine and protein amines. The reduced direct water saturation led to stronger CEST effects at 2 ppm (Figure 10C). In GM in the center slice, the mean and standard error MTR asym values at 2 ppm for the HSExp pulse were 3.98% ± 0.025%, 3.23% ± 0.024%, and 2.14% ± 0.025% for 3, 2.5, and 2 µT, respectively. For the rectangular saturation pulses, the MTR asym values were 3.21% ± 0.022%, 2.62% ± 0.023%, and 1.56% ± 0.018% for 3, 2.5, and 2 µT, respectively. In WM, the mean MTR asym values in the center slice were 2.02% ± 0.022%, 1.35% ± 0.019%, and 0.19% ± 0.02% for 3, 2.5, and 2 µT, respectively. In both tissues, this difference was found...
significant based on a multicomparison corrected analysis of variance. The stronger CEST effect was also visible in the MTR$_{\text{asym}}$ image at 2 ppm (Figure 10B,D), especially in GM areas.

**FIGURE 8** C, Glucose phantom measurement using HSExp pulses for different glucose concentrations. The 1st, 2nd, and 3rd row show the results for 5, 3, and 1 µT saturation pulses, respectively. A,E,I, The first column shows the MTR$_{\text{asym}}$ in three different glucose concentrations (100, 50, and 25 mM). The 2nd column shows the on-resonant $T_1^{\rho w}$-images of the HSExp pulse (B,F,J), the 3rd column shows the $T_1^{\rho w}$-images of the HSExp pulse at 1.3 ppm (C,G,K), the 4th column shows the MTR$_{\text{asym}}$ images at 1.3 ppm (D,H,L). The relative $B_1$ map (N) and the $\Delta B_0$ map [ppm] (O). F, At 3 µT, the on-resonant image shows artifacts in regions with low $B_1$. J, At 1 µT, the adiabatic condition is heavily violated leading to severe artifacts in the on-resonant image. C,G,K, The images at 1.3 ppm are free of oscillation artifacts for all $B_1$ amplitudes. M, The MTR$_{\text{asym}}$ (1.3 ppm) as a function of $B_1$ is shown for both the Gaussian and the HSExp pulse. For $B_1 > 2$ µT MTR$_{\text{asym}}$ from the HSExp pulse is higher compared with the Gaussian pulse: at maximum labeling the HSExp pulse yields ~1.3 times the CEST effect obtained with Gaussian pulse. The error bars indicate the standard deviation in the ROI. The high MTR$_{\text{asym}}$ values at approx. 0.13 ppm for the Gaussian pulse are due to oscillation imaging artifacts.

**4 | DISCUSSION**

In this work, we presented an adiabatically prepared constant-amplitude SL pulse, usable for on- and off-resonant
T1\textsuperscript{ρ} imaging and Z-spectroscopy at UHF. The acquired continuous Z-spectra in vivo showed very little artifacts compared with commonly used techniques, such as unmatched HS SL pulses\textsuperscript{6} in the on-resonant case or conventional Gaussian or rectangular CEST pulses in the off-resonant case. We want to point out that the applied amplitude (B1 ≈ 5 µT) is not low in terms of CEST imaging (often 0.5 µT to 4 µT),\textsuperscript{2} but low compared with the typical SL amplitudes (5–40 µT)\textsuperscript{6,25}; thus, all experiments could be performed within the SAR and hardware limits at 9.4 T. As such a “low” power approach is especially beneficial for chemical exchange weighting of on- and off-resonant SL as stated in Jin and Kim\textsuperscript{26} and again herein, we provide a method for robust on- and off-resonant T1\textsuperscript{ρ} measurements as well as continuous Z-spectra acquisition with strong exchange weighting and intrinsically low direct water saturation which is also feasible for human brain scans at 9.4 T.

Many different approaches exist in the field of on- and off-resonant T1\textsuperscript{ρ}-imaging, with both adiabatic and nonadiabatic approaches. In an early work, Santyr et al\textsuperscript{27} used off-resonant SL pulses for breast cancer imaging at 1.5 T. Although they could show that adiabatic pulses are superior compared to classical SL pulses, their approach was based on a relatively long frequency modulation (30 ms) without amplitude modulation. A combination of on- and off-resonant adiabatic SL pulses was presented by Gröhn et al\textsuperscript{25} who showed a positive T1\textsuperscript{ρ}-contrast for cerebral ischemia in vivo with high-field MRI. However, very high B1 amplitudes were used (B1 ≥ 40 µT), which can only be applied in animal experiments, because the SAR limit would be exceeded for humans. Going to UHF MRI, Jin and Kim\textsuperscript{15} presented off-resonant SL imaging at 9.4 T. With a conventional SL approach, they showed that the sensitivity and selectivity is higher in chemical exchange SL than in a classical CEST experiment. Although they were using a low B1 power, the conventional SL approach requires the homogeneous B0 and B1 fields achievable in an animal scanner. Recently Schuenke et al\textsuperscript{6} presented an approach for on-resonant adiabatic SL imaging in humans at 7 T with a locking power of B1,lock = 5 µT and adiabatic pulse power of B1,adia ≈ 20 µT. This approach works well for on-resonant SL imaging and showed glucose hydroxyl exchange weighting in vivo\textsuperscript{7,28} based on the change of R2\textsubscript{ex} in a tumor ROI of approximately 0.55 Hz after a glucose injection. However, the mismatch between the AHP and the rectangular locking pulse disables the possibility for off-resonant SL imaging. One approach to overcome this amplitude mismatch is to implement a ramp in the amplitude modulation, that takes B1,max from the AHP pulse to the value of the locking pulse, as presented in Gröhn et al.\textsuperscript{29} Jin and Kim\textsuperscript{30} implemented this approach at UHF; however, the B1 amplitude in both studies was comparatively high (12–40 µT).

The presented approach is actually a generalization of the approach of Schuenke et al.\textsuperscript{6} By adjusting the adiabatic pulse shape, a HS SL pulse with matching amplitude could
be designed to achieve both on- or off-resonant SL features. The presented work mainly focused on creating a pulse shape that is able to create images with as little artifacts as possible. While the measured signals showed smooth $T_1$-decay, the $T_1$-time is a function of both $\Delta \omega$, and $\omega_1$ and, therefore, also exhibits a modulation following the $B_0$ and $B_1$ inhomogeneity. However, intrinsic $B_0$ and $B_1$ weighting can be compensated for, similar to $B_0$ and $B_1$ correction in CEST imaging.23

We want to point out that $B_1$ and $B_0$ compensation techniques are also available with conventional SL pulses. A good overview about correction techniques is given by Chen et al31 However, this work includes only non-adiabatic approaches like rotary echo SL,32,33 composite pulses,34 or phase-cycled composite SL methods. Although, off-resonant correction methods were proposed, the presented approaches used high amplitude $B_1$ pulses, which would exceed the amplifier limit in our case. It might be possible to achieve similar performance with non-adiabatic approaches, which would be helpful in terms of SAR limitations, but this requires a comprehensive comparison and has to be studied in detail. The matched adiabatic SL approach has the benefit that it is also very simple to implement as it is exactly the same amplitude and frequency pulse shape and only the frequency offset is changed. Thus, it is not necessary to adjust the flip angle to the frequency offset, as is required in conventional SL approaches.

As shown in the Theory section in Equations (13) and (14), $R_{1p}$ cannot simply be separated in $R_{eff}$ and $R_{ex}$, as pure $R_{1w}$ and $R_{2w}$ are unknown. In the following, the observed relaxation rates $R_{1,obs}$ and $R_{2,obs}$ and the $R_{eff,obs}$ value proposed in Equation (16) are used for comparison.

During the on-resonant $R_{1p}$ measurement, the relative $B_1$ was $rB_1$,$GM$ =98.24% in the GM ROI and $rB_1$,$WM$ =91.85% in the WM ROI. The $B_0$ shift was $\Delta \omega$,$GM$ = 0.0767 ppm in the GM and $\Delta \omega$,$WM$ = 0.0901 ppm in the WM ROI. With $\theta = \arctan(\omega_1 / \Delta \omega)$ this yields a mean $\theta$,$GM$ = 83.56° and $\theta$,$WM$ = 81.92°. Assuming literature values for $R_{1,obs}$,$GM$ =0.5 Hz, $R_{2,obs}$,$GM$ =28.57 Hz, $R_{1,obs}$,$WM$ =0.7 Hz, and $R_{2,obs}$,$WM$ =33.81 Hz at 9.4 T,35 this leads to theoretical values of $R_{eff,obs}$,$GM$ =28.22 Hz and $R_{eff,obs}$,$WM$ =33.68 Hz. The measured values of $R_{1p}$ in this study with $R_{1p}$,$GM$ =18.72 ± 0.76 Hz and $R_{1p}$,$WM$ =21.52 ± 0.64 show, therefore, a discrepancy.
of approximately 10 Hz. Thus, \( R_{\text{eff,obs}} \) incorporates exchange contributions of \( R_{2,\text{obs}} \) and consequently \( R_{1p} \) includes fewer \( R_{\text{ex}} \) contributions leading to slower relaxation. This result is in accordance with the simulation of \( R_{\text{eff,obs}} \) (Figure 3C), as we expect \( R_{1p} < R_{\text{eff,obs}} \) for \( \Delta \omega = 0 \) Hz. In comparison to previous work, the on-resonant \( R_{1p} \) map showed in Schuenke et al.\(^6\) which was acquired at 7 T using an HS SL pulse, showed a discrepancy in the same range: the measured \( R_{1p} \) in WM in their study was approximately 18 Hz, whereas \( R_{\text{eff,obs,WM}} \), assuming \( \theta_{\text{WM}} = 90^\circ \), would be approximately 27 Hz according to Zhu et al.\(^{35} \) In MRI studies of human cartilage, the measured on-resonant \( R_{1p} \) was also smaller than \( R_2 \).\(^{36} \) A detailed investigation in on-resonant \( R_{1p} \) relaxation times in the human brain would be desirable in the future.

In the off-resonant case the measured \( R_{1p} \) was 10.68 ± 0.48 Hz for GM and 11.36 ± 0.37 Hz for WM in the center slice. An offset of 1 ppm including \( B_1 \) and \( B_0 \) inhomogeneity results in a mean \( \theta_{\text{GM}} = 32.25^\circ \) and \( \theta_{\text{WM}} = 30.23^\circ \). This leads to \( R_{\text{eff,obs,GM}} = 8.48 \text{ Hz} \) and \( R_{\text{eff,obs,WM}} = 9.26 \text{ Hz} \), again using literature values for GM and WM.\(^{35} \) Interestingly, in the off-resonant case \( R_{1p} \) has values above the theoretical \( R_{\text{eff,obs}} \). Again, this result is in accordance with the simulation of \( R_{\text{eff,obs}} \) (Figure 3C), as we would expect \( R_{1p} > R_{\text{eff,obs}} \) at \( \Delta \omega = 1 \) ppm. It seems that off-resonant, \( R_{\text{ex}} \) contributions dominate \( R_{1p} \) as the \( R_2 \) contribution is suppressed by the \( \sin^2(\theta) \) term. Also the \( R_{\text{ex}} \) contribution increases if the irradiation frequency offset is closer to \( \delta_{\omega b} \) (Equation 10), usually located on the positive side of the \( \Delta \omega \)-axis, which cannot be expressed by \( R_{\text{eff,obs}} \).

Further quantitative investigation of the full \( R_{1p} \)-spectrum is now enabled for in vivo applications and can be investigated in forthcoming studies. Comparing on- and off-resonant SL not only for different saturation powers, but also for different \( B_0 \) field strengths might yield deeper insights into these observations.

As shown in Figure 10, the \( MTR_{\text{asym}} \) values at 2 ppm showed a difference of around 20% between the HSExp and the rectangular pulse. As the applied \( B_1 \) was 2.5 µT, the angle \( \theta \) is small and we would, therefore, expect comparable \( MTR_{\text{asym}} \) values in the same range for both pulses, as \( MTR_{\text{Asym,CEST}} = \cos(\theta) \cdot MTR_{\text{Asym,SL}} \).\(^{12,26} \) For an amplitude of 2.5 µT, this would only result in a difference of approximately 1% at 2 ppm. Thus, the larger difference is unexpected, but can have several explanations. First, there could be some labeling during the frequency sweep of the adiabatic pulse affecting other CEST-active metabolites. Second, the asymmetry in vivo still has contributions from both sides of the spectrum. Although at the low applied power the CEST effect from faster exchanging groups is enhanced, the slower exchanging NOE at negative frequencies still contributes and reduces the \( MTR_{\text{asym}} \). Thus, it could be that CEST labels the NOEs more strongly than chemical exchange SL. While these two arguments address the labeling, the most obvious difference is the reduced direct water saturation in the spectra. Thus, a third explanation might be that the magnetization vector after a rectangular pulse, which is only 100 ms long, is not aligned with the effective field and still has some residual oscillation component (see Figure 1A). This can lead to stronger direct saturation. These influences of SL pulses on spillover and labeling could explain the relatively large difference in \( MTR_{\text{asym}} \). However, these effects must be further investigated for quantification of exchange mechanisms in the \( R_{1p} \)-spectrum.

We do not claim the proposed HSExp pulse to be the optimal pulse shape for constant-amplitude adiabatic SL applications. This study was rather a feasibility test of whether we can implement a stable, matching amplitude low-power adiabatic SL pulse at UHF. By investigating a new mathematical function for the pulse shape with more degrees of freedom and using simulations for parameter optimization, we were able to find a reasonable shape for our applications. However, we think that the pulse design can still be improved. Potential considerations for finding optimal pulse parameters could be Shinnar-LeRoux-algorithms\(^{37} \) or optimal control approaches\(^{38,39} \) using the desired \( T_{1p} \)-dominated \( Z \)-spectrum as part of the design criteria. The present study shows that this optimization can be run with a matched pulse and the boundary conditions of \( B_1 = 5 \text{ µT} \) and \( t_{\text{adia}} = 8 \text{ ms} \). With future optimizations, both \( B_1 \) and \( t_{\text{adia}} \) can potentially be further decreased.

Finally, if the desired application requires off-resonant saturation at frequencies \( |\Delta \omega| > 100 \text{ Hz} \) and \( B_1 \) power below 5 µT, conventional shaped pulses perform very well and are simpler to implement and use.

5 | CONCLUSION

By adapting the pulse shape of the adiabatic half passage pulse, we were able to acquire robust on- and off-resonant SL prepared \( T_{1p} \)-weighted images. Both on-resonant \( T_{1p} \) images as well as off-resonant CEST images showed only minor artifacts despite large field inhomogeneity at 9.4 T. Furthermore, the chemical exchange weighting was higher with the proposed pulse compared with conventional CEST methods. The proposed pulse is a proof-of-principle that matched adiabatic pulses can be used for improved CEST preparation at \( B_1 \) powers as low as 3 µT, and suggests that further optimization of SL pulses for different field strengths and applications are possible.

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