Purpose: To enable whole-brain quantitative CEST MRI at ultra-high magnetic field strengths ($B_0 \geq 7T$) within short acquisition times.

Methods: Multiple interleaved mode saturation (MIMOSA) was combined with fast online-customized (FOCUS) parallel transmission (pTx) excitation pulses and $B_1^+$ correction to achieve homogenous whole-brain coverage. Examinations of 13 volunteers were performed on a 7T MRI system with 3 different types of pulse sequences: (1) saturation in circular polarized (CP) mode and CP mode readout, (2) MIMOSA and CP readout, and (3) MIMOSA and FOCUS readout. For comparison, the inverse magnetic transfer ratio metric for relayed nuclear Overhauser effect and amide proton transfer were calculated. To investigate the number of required acquisitions for a good $B_1^+$ correction, 4 volunteers were measured with 6 different $B_1$ amplitudes. Finally, time point repeatability was investigated for 6 volunteers.

Results: MIMOSA FOCUS sequence using $B_1^+$ correction, with both single and multiple points, reduced inhomogeneity of the CEST contrasts around the occipital lobe and cerebellum. Results indicate that the most stable inter-subject coefficient of variation was achieved using the MIMOSA FOCUS sequence. Time point repeatability of MIMOSA FOCUS with single-point $B_1^+$ correction showed a maximum coefficient of variation below 8% for 3 measurements in a single volunteer.

Conclusion: A combination of MIMOSA FOCUS with a single-point $B_1^+$ correction can be used to achieve quantitative CEST measurements at ultra-high magnetic field strengths ($B_0 \geq 7T$) within short acquisition times.
1 | INTRODUCTION

CEST MRI\(^1\) uses selective labeling of macromolecular protons during fast T\(_1\)-weighted imaging. Through the exchange of the labeled protons with free water protons, the metabolic environment in vivo can be investigated. Image contrasts that depend on specific metabolic groups, such as amine (NH\(_2\)) or hydroxyl (OH) groups can be achieved through the analysis of a water saturation spectrum called the Z-spectrum.

Although CEST MRI does work at typical clinical field strengths of 3T,\(^2\) CEST MRI largely benefits from ultra-high field (UHF) strengths (B\(_0 \geq 7\)T). This is caused by both higher SNR and higher spectral resolution, resulting in improved separation of the different metabolites appearing in the Z-spectrum. Several current studies, presenting the potential for tumor grading and treatment response prediction, are using UHF systems.\(^5\)\(^-\)\(^8\)

Until recently, a major factor limiting the application of CEST imaging in clinical studies was the long acquisition time required for whole-brain CEST (WB-CEST) MRI. Therefore, CEST studies were often performed as 2D acquisitions with a small number of acquired slices. Recent improvements in sampling schemes\(^9\)\(^-\)\(^14\) enable a fast and robust readout of whole-brain data. The current WB-CEST acquisition methods range from multi-shot 3D gradient echo sequences (GRE) sequences\(^10\)\(^,\)\(^13\) through single-shot GRE\(^9\) and EPI sequences\(^11\)\(^,\)\(^14\) up to gradient and spin echo sequences.\(^12\) At UHF, however, the inhomogeneity of the transmit field (B\(_1^+\)) renders quantitative CEST MRI challenging, because the local effective B\(_1^+\) strongly influences the magnitude of the CEST contrast.\(^15\)\(^,\)\(^16\) Therefore, retrospective correction\(^17\)\(^-\)\(^19\) or mitigation\(^20\)\(^-\)\(^22\) of B\(_1^+\) inhomogeneity is required. This applies even more for WB-CEST MRI than for 2D acquisitions. In whole-brain measurements, the local effective B\(_1^+\) varies between relative B\(_1^+\) (rB\(_1\)) values of approximately 0.1 and 1.5.\(^11\) Results by Akbay et al\(^11\) indicate that the inverse magnetic transfer ratio metric (MTR\(_{\text{rex}}\)) of relayed nuclear Overhauser effect (rNOE) and amide proton transfer (APT) can be corrected without introducing major errors only in regions with sufficiently high rB\(_1\) of over 0.5. As a result, a new method that reduces the variation of the rB\(_1\) is necessary to introduce quantitative CEST measurements at 7T into clinical studies.

Mitigation of this high variation of rB\(_1\) in CEST was achieved in previous works through the application of dielectric pads\(^10\)\(^,\)\(^13\) or parallel transmit (pTx) systems.\(^20\)\(^-\)\(^22\) Unfortunately, dielectric pads achieve only partial mitigation of the B\(_1^+\) inhomogeneity. Therefore, they are applicable mostly for correction of small regions. Mitigation of the B\(_1^+\) inhomogeneity with the use of a pTx system can be achieved through B\(_1\) shimming\(^23\) and transmit SENSE\(^24\)\(^,\)\(^25\) B\(_1\) shimming uses modulation of phase and amplitude for each transmitter channel, further called a mode. The interference of the modulated RF pulses allows mitigation of the B\(_1^+\) inhomogeneity in a certain region. At the same time, B\(_1\) shimming usually results in decreased B\(_1^+\) homogeneity outside a small target region. Because of this tradeoff, it is extremely hard to achieve a fully homogenous B\(_1^+\) distribution in the whole-brain.\(^23\) A potential solution to this problem is the application of transmit SENSE\(^24\) in which not only the amplitude and phase of each transmitter channel is varied, but also RF pulse duration, shape, and trajectory in the transmit k-space, resulting in improved control over the spatial distribution of the flip angle (FA). However, this method requires additional calculation of the applied pulses directly before the measurement, which complicates clinical translation. Transmit SENSE was previously applied for CEST with its respective disadvantages of long calculation times.\(^20\)

The recently presented multiple interleaved mode saturation (MIMOSA)\(^23\) omitted the homogeneity problems of B\(_1\) shimming through the application of 2 interleaved modes. The first mode used is the circular polarized (CP) mode in which the phase of each transmitter channel is shifted by 360°/N where N is the number of transmitter channels. The second mode applied is the 90° mode in which the phases are shifted by 360°/N. The B\(_1^+\) fields of these 2 modes are spatially complementary to each other. As a result, the mean saturation B\(_1^+\) field becomes more homogenous. As such, in comparison to transmit SENSE, MIMOSA does not require a subject-specific optimization. However, in our recent work,\(^26\) we presented that this distribution is not fully homogenous over the whole-brain. Hence, B\(_1^+\) correction can be omitted only in the central part of the brain in a volume of approximately 230 × 230 × 40 mm\(^3\). Outside this region, B\(_1^+\) correction seems to be still necessary.

strengths. Compared to previous B\(_1^+\) correction methods, acquisition time can be reduced as additional scans required for B\(_1^+\) correction can be omitted.

KEYWORDS

7T, chemical exchange saturation transfer, fast-online customized pulses, multiple interleaved mode saturation, parallel transmission, spiral non-selective trajectory
Until now, we discussed the potential correction and mitigation methods applied to the saturation part. However, the CEST contrast is also influenced by the $B_1^+$ inhomogeneity of the readout, which is neglected in most correction and mitigation methods. A spatial variation of the readout FA leads to 2 effects in case of CEST acquisitions. On one hand, it introduces a spatial variation of the SNR of the images; on the other hand, it directly influences the measured CEST contrast. Both effects become visible in certain parts of the brain where the CEST contrast still occurs noisy or is inhomogeneous, even though $B_1^+$ correction and mitigation methods were applied.

In this work, we propose a WB-CEST MRI that combines MIMOSA with a spiral-centric reordered-square readout pattern\(^9\) with fast online-customized (FOCUS) pTx excitation pulses\(^{27}\) to achieve fast and highly homogenous CEST MRI contrast. Comparisons of the sequence to a sequence applying CP mode in both saturation and excitation, and to a pulse sequence using MIMOSA and CP excitation are presented in both phantom and in vivo acquisitions. The number of required measurements for $B_1^+$ correction is investigated for the MIMOSA FOCUS sequence. Additionally, inter-subject and inter-session repeatability are analyzed.

2 | METHODS

2.1 | Measurement system

All measurements were conducted on a 7T whole-body MR system (MAGNETOM Terra, Siemens Healthcare GmbH, Erlangen, Germany) using an 8Tx/32Rx head coil (Nova Medical, Wilmington, MA).

2.2 | Phantoms and volunteers

For phantom measurements, a $21 \times 21 \times 29$ cm\(^3\) glass head was filled with Skyr—fresh sour milk cheese (Milsani brand, Germany). The use of Skyr was motivated by its Z-spectrum showing APT, rNOE, and MT effects. This fact allows for the use of the same reconstruction pipeline as for the in vivo data.

Twenty-three healthy volunteers (31 ± 9 years old.; female: $n = 11$) were recruited under the approval of the local ethics committee. All volunteers were provided with a full description of the study and have signed informed consent to participate in the study.

2.3 | CEST imaging: saturation

WB-CEST MRI was performed using a pulsed CEST GRE sequence.\(^9,28\) For the Gaussian pre-saturation pulse train, MIMOSA was applied as presented in previous work.\(^{21}\)

For all measurements, the same frequency offsets were chosen. All saturation parameters were kept constant except for the $B_1$ amplitude and can be found in the Supporting Information “Measurement Parameters” section together with a list of the 56 measured offsets.

2.4 | CEST imaging: readout

FOCUS pTx pulses as described in Herrler et al\(^{27}\) were used to homogenize the FA distribution of the readout. These pulses combine the concept of “Universal Pulses”\(^{29}\) with a fast subject-specific online optimization of the pTx excitation pulses. The k-space trajectory of the FOCUS pulses is based on a spiral-nonselective (SPINS) trajectory.\(^{30}\) This trajectory was optimized offline based on a training data set of whole-head $B_0$ and $B_1$ maps previously acquired from 20 healthy European subjects.\(^{27}\) Subsequently, the resulting Universal Pulse trajectory was used as an initial guess during an online customization step for each subject. A pulse duration of 0.5 ms was chosen to enable short TE and TR. To evaluate the performance of the FOCUS pulses, the simulated FA distributions in the brain of 28 healthy subjects (not used for the optimization) were analyzed. The average FA normalized root mean square error (NRMSE) of the tailored pulse, over these volumes, was 8.20%. Maps of the FA distribution of the FOCUS excitation pulse for each measurement were retrospectively simulated based on $B_1^+$ coil profiles acquired for the online optimization. To perform a fast whole-brain acquisition, we used a Cartesian spiral-centric reordered GRE sequence.\(^9\) For excitation, 2 different pulses were compared: (1) the above-described 0.5-ms tailored FOCUS pTx pulse, and (2) a 0.1-ms long rectangle pulse in CP mode, which corresponds to a traditional 1 Tx readout excitation. These 2 readout pulses were combined with MIMOSA saturation, creating the MIMOSA FOCUS and MIMOSA CP sequences accordingly. Additionally, measurements with CP mode saturation and CP mode readout were performed (Full CP). Schematic depiction of the 3 compared sequences can be found in Figure 1. One single CEST acquisition took 6 min 14 s and the acquisition parameters are presented in the Supporting Information “Measurement Parameters” section.

2.5 | Image coregistration

For each in vivo CEST acquisition, the volume of each offset was registered on the $M_0$ volume using the Elastix framework.\(^{31-34}\) A linear interpolation of the movement between the offsets of $-0.6$ ppm and $+0.6$ ppm was performed to avoid the coregistration of low-intensity images.
2.6 | B₀ correction

For all of the measurements, a B₀ map was calculated based on the minimal value of the Z-spectrum, acquired for every B₁⁺ power. B₀ correction was applied as described by Zaiss et al.³⁵

2.7 | CEST reconstruction

The acquired and B₀ corrected CEST data were fitted pixel-wise with a 5-pool (water, amide, amine, rNOE, and MT) Lorentzian model as described by Windschuh et al.¹⁸ The exact fitting parameters of the Lorentzian model can be found in Supporting Information Table S1. Based on these results, a reference (Z_ref) and a label spectrum (Z_lab) were obtained. The MTR_Rex contrast for rNOE and APT was calculated as described by Zaiss et al and Windschuh et al¹⁸,³⁶ as:

\[
MTR_{Rex}(Pool) = \frac{1}{Z_{lab}(\delta_{Pool})} - \frac{1}{Z_{ref}(\delta_{Pool})}.
\]

2.8 | B₁⁺ correction

After calculation of MTR_Rex, a contrast-based linear B₁⁺ correction, as described by Windschuh et al,¹⁸ was applied. B₁⁺ maps used for the correction were acquired for both CP and 90° mode²¹ using a pre-saturated 2D turbo-flash sequence.³⁷ Its acquisition parameters are presented in the Supporting Information “Measurement Parameters” section.

For B₁⁺ correction of MIMOSA CEST images, rB₁ values were calculated based on the B₁ continuous wave power equivalent²¹,³⁸ according to the following equation:

\[
rB_{1,MIMOSA}(r) = \sqrt{rB_{1,CP\, mode}(r)^2 + rB_{1,90\,^\circ\, mode}(r)^2},
\]

2.9 | T₁-weighted imaging, segmentation and histogram evaluation

Whole-brain T₁-weighted imaging was performed using a FOCUS MPRAGE sequence (acquisition parameters are shown in the Supporting Information “Measurement Parameters” section). The resulting images were segmented into white and gray matter with use of SPM.³⁹ The high-resolution segments were registered onto the M₀ images of...
each of the 3 CEST methods. For each investigation, and both tissue types, histograms of the MTR_{Rex}(APT) and MTR_{Rex}(rNOE) contrasts were calculated and fitted with a Gaussian curve. The within-subject coefficient of variation (wCoV) for each volunteer was calculated as $wCoV = \frac{\sigma}{\mu}$, where $\sigma$ is the SD and $\mu$ is the mean of the fitted Gaussian curve.

2.10  |  Sequence comparison

A comparison between the current standard (Full CP) and the 2 MIMOSA sequences (MIMOSA CP and MIMOSA FOCUS) was performed. To compare the tSNR between the different sequences, 3 volunteers were scanned with each method. For each volunteer, 55 measurements at a single offset of 3.5 ppm were acquired. All of the measurements were registered onto the 10th measurement. The tSNR was calculated as the ratio of mean to SD in each voxel over 35 measurements in a row. The 35 measurements were chosen based on their structural similarity index to avoid outliers because of strong movement or physiological variations.  

The SNR for all acquisitions was calculated based on 150 pseudo-replicas of the first M_0 image of each acquisition. Thirteen volunteers (male $n = 6$, female $n = 7$) and a phantom were examined to compare the 3 different types of pulse sequences (full CP, MIMOSA CP, and MIMOSA FOCUS). For these acquisitions, B_1 amplitudes ($B_1 = \frac{\gamma n}{\gamma_{CP}}$) of 0.7 $\mu$T and 1.1 $\mu$T were chosen. For each volunteer, each method, and both contrasts (MTR_{Rex}(rNOE), MTR_{Rex}(APT)), mean value and SD in both segments (SPM-segmented WM and GM regions) were calculated. The spatial variability of the sequences was investigated through calculation of the wCoV of MTR_{Rex}(APT) and MTR_{Rex}(rNOE) in both GM and WM. The inter-subject repeatability was investigated through the calculation of the coefficient of variation (CoV) of the $\mu$ value of MTR_{Rex}(APT) and MTR_{Rex}(rNOE) in GM and WM over the 13 volunteers, which is later referred to as inter-subject CoV (iCoV). To test for significant differences between 2 methods, a paired $t$ test was applied.

2.11  |  Investigation of MIMOSA FOCUS sequence with $B_1^+$ correction

First, the stability of the MIMOSA FOCUS sequence with respect to the $B_1^+$ correction methods was investigated. For this purpose, the performance of the $B_1^+$ correction method with different numbers of correction points was examined. Hence, 4 volunteers were measured using 6 different B_1 values during the saturation, ranging between 0.6 $\mu$T and 1.1 $\mu$T with a step size of 0.1 $\mu$T. Contrast-based $B_1^+$ correction with different numbers ($N_{corr} = 1$ to 6) of B_1 amplitudes was applied.

After this, the time point repeatability of the sequence with the 1-point $B_1^+$ correction method was investigated. For this purpose, 2 female and 4 male volunteers were measured 3 times on the same day with the MIMOSA FOCUS sequence with $B_1 = 0.7$ $\mu$T. Between the measurements, the volunteers were asked to slightly change their position and B_0 and B_1 adjustments were performed anew. The time point repeatability was evaluated based on the CoV of the $\mu$MTR_{Rex}(rNOE) and $\mu$MTR_{Rex}(APT) for each of the 3 measurements.

3  |  RESULTS

3.1  |  Sequence comparison

Figure 2 shows the rB_1 maps of the saturation, FA maps of the readout, and SNR of all 3 compared sequences in a phantom measurement. The rB_1 maps of the MIMOSA saturation show an increase in homogeneity (Figure 2B,C), although regions of low rB_1 (rB_1 < 0.5) are still present in these acquisitions. A major increase of both the homogeneity and mean of the readout FA can be observed in the MIMOSA FOCUS sequence. In areas where the CP mode readout shows low rB_1 values (rB_1 < 0.5) (Figure 2F), an artifact in the FA maps of the MIMOSA FOCUS sequence is visible. It is caused by the retrospective FA map simulation with the use of CP mode based $B_1^+$ coil profiles. A nearly 2-fold increase in SNR can be observed for the MIMOSA FOCUS sequence (Figure 2I, Supporting Information Table S2). Regions with higher SNR correspond to regions with higher readout FA.

Figure 3 shows a comparison of phantom measurements in which MTR_{Rex}(rNOE) and MTR_{Rex}(APT) contrasts were calculated for the 3 sequences after $B_1^+$ correction with $N_{corr} = 1$ and 2. For the full CP method, both contrasts are increased around the area that had extremely high rB_1 (rB_1 > 1.2) during the saturation (Figure 2A). This effect is strongly reduced for both sequences using the MIMOSA saturation (Figure 3 2nd and 3rd column). In the areas that correspond to low rB_1 values (rB_1 < 0.5) in the MIMOSA saturation maps differences between MTR_{Rex}(rNOE) and MTR_{Rex}(APT) maps corrected with $N_{corr} = 1$ and $N_{corr} = 2$ can be noticed. An increased blurring is visible in the outer regions of the phantom for the MIMOSA FOCUS sequence. This is correlated to the higher FA that leads to an increase in the width of the point spread function (PSF) (see simulations in Supporting Information Figures S1-S3).

Figure 4 shows the rB_1 maps of the saturation, FA maps of the readout, and tSNR and SNR of all 3 compared sequences for a single volunteer. Additionally, a statistical
evaluation of the mean and wCoV of the rB1, FA, SNR, and tSNR is presented in Table 1. Measurements applying MIMOSA show rB1 values varying between rB1 ≈ 0.6 and 1.0 over the whole volume of the brain (Figure 4B,C). Compared to CP mode saturation (Figure 4A; rB1 ≈ 0.1 and 1.5), this is a major increase in B1 homogeneity. Comparable to the phantom measurements a notable increase in the mean FA and SNR can be observed for the MIMOSA FOCUS sequence (Figure 4I, Table 1). This is especially in the area of the cerebellum, where extremely low FA values (FA ≈ 1°-2°) of the CP readout can be noted (Figure 4D-E). A slight increase in tSNR can also be observed in the acquisitions with MIMOSA FOCUS. In some cases, the tSNR maps show ringing artifacts (Figure 4K, Supporting Information Figure S6). No increase in SNR (Figure 4H) occurs in the MIMOSA CP sequence in comparison to the Full CP sequence (Figure 4G,J). A slight hemispheric asymmetry is visible in some of the SNR and tSNR acquisitions (Figure 4L and Supporting Information Figure S5H,I,K,L). The mean value and SD of the tSNR for each method and all 3 volunteers are presented in Supporting Information Table S3. Quantitative evaluation of the FA NRMSE in both phantom and in vivo shows that the mean FA distributions of both the MIMOSA saturation and the FOCUS pulse are significantly smaller compared to CP mode (Supporting Information Table S4).

Figure 5 shows a comparison of MTRRex(rNOE) and MTRRex(APT) contrasts calculated for the 3 compared sequences in vivo. For both contrasts, acquisitions with CP mode readout show an increased noise around the cerebellum and occipital lobe (Figure 5 1st and 2nd column). This is in agreement with regions of low SNR shown in Figure 4. Full CP acquisitions additionally show an overestimation of the MTRRex(APT) values in this area for acquisitions with both Ncorr = 1 and Ncorr = 2 (Figure 5G,J). At the same time, an underestimation of the MTRRex(rNOE) values occurs for acquisitions with Ncorr = 1 (Figure 5A). Both of these effects can be correlated to the extremely low values of rB1 (rB1 < 0.5) during the saturation (Figure 4A).

The in vivo MIMOSA FOCUS acquisitions show, similar to the phantom acquisitions, an increased blurring (Figure 5, 3rd column). A comparable blurriness of the images is visible also in the Full CP and MIMOSA CP acquisitions in the central part of the brain, where a high FA (FA > 7°)
of the readout occurs. As for the phantom, the increased blurring and SNR correlate with an increase of the width of the PSF because of an increase of the FA (Supporting Information Figures S1-S3). Accordingly a variation of the readout FA of the FOCUS pulses results in a change of the mean SNR and blurriness (Supporting Information Figure S4 and Supporting Information Table S5). Using a readout FA matching the mean FA of the CP mode readout results in an SNR and blurring comparable to CP mode acquisitions. Such an adjustment does not influence the achieved homogeneity of both the readout FA distribution and the MTR$_{\text{Rex}}$ contrasts of the MIMOSA FOCUS sequence (Supporting Information Figures S5 and Supporting Information Table S6). Even with an adjusted FA an increase of the SNR around the cerebellum and the occipital lobe can be noted.

For both MTR$_{\text{Rex}}$(rNOE) and MTR$_{\text{Rex}}$(APT) of MIMOSA FOCUS, no major differences between $B_1^+$ correction with $N_{\text{corr}} = 1$ and $N_{\text{corr}} = 2$ can be observed. Both methods show a more homogenous distribution of the MTR$_{\text{Rex}}$ values in comparison to acquisitions with CP mode readout.

3.2 | Statistical evaluation

In Figure 6 an investigation of the wCoV for all 13 volunteers is presented for all 3 sequences without and with $B_1^+$ correction applying $N_{\text{corr}} = 1:2$. A decrease of the mean wCoV can be observed for the MIMOSA FOCUS acquisitions with $B_1^+$ correction (Figure 6) in comparison to both acquisitions with CP mode readout. Additionally, the stability of the
A major increase in $B_1^+$ homogeneity of the readout can be observed for MIMOSA FOCUS. In addition, MIMOSA FOCUS results show an increase in SNR and tSNR. This increase correlates with the increase of the readout FA. For both sequences applying CP readout (1st and 2nd column) a decrease of the SNR and tSNR can be observed in the cerebellum and around the occipital lobe.

**TABLE 1** Evaluation of the mean ± SD of the mean value ($\mu$) and wCoV of $rB_1$, FA, SNR, and tSNR in the brain volume for the 3 compared methods.

| Sequence   | CP mode | MIMOSA CP | MIMOSA FOCUS |
|------------|---------|------------|--------------|
| Value      | $\mu$  | wCoV (%)  | $\mu$  | wCoV (%) | $\mu$  | wCoV (%) |
| Saturation | $rB_1$  | 0.71 ± 0.03 | 24.6 ± 2.4 | 0.78 ± 0.02 | 13.2 ± 0.5 | 0.78 ± 0.02 | 13.2 ± 0.5 |
| Readout FA | 4.98° ± 0.2° | 24.6 ± 2.4  | 4.98° ± 0.2° | 24.6 ± 2.4  | 6.90° ± 0.02° | 11.2 ± 1.5 |
| SNR        | 318 ± 25  | 52.4 ± 4.2  | 310 ± 21  | 49.0 ± 4.3  | 400 ± 31  | 46.0 ± 3.6  |
| tSNR       | 169 ± 18  | 37.1 ± 3.1  | 179 ± 47  | 36.0 ± 3 | 206 ± 32  | 32 ± 1.6  |

Abbreviations: CP, circular polarized; FOCUS, fast online-customized sequence; MIMOSA, multiple interleaved mode saturation; wCoV, within-subject coefficient of variation.

The mean and SD were calculated over 13 volunteers and in case of tSNR over 3 volunteers. An increase of the readout $\mu$FA can be observed for the MIMOSA FOCUS sequence. The MIMOSA CP and MIMOSA FOCUS sequence show a decreased mean wCoV($rB_1$). In general, a decrease in the mean wCoV can be observed for the MIMOSA FOCUS sequence.
wCoV, which is depicted by the boxplot size, increases for the MIMOSA FOCUS sequence.

The box plots shown in Figure 7 provide a comparison of the $\mu\text{MTR}_{\text{res}}(\text{rNOE})$ and $\mu\text{MTR}_{\text{res}}(\text{APT})$ within the WM and GM segments over all 13 subjects. For both contrasts and both tissue types, MIMOSA FOCUS proves to have a comparable inter-subject mean value and comparable iCoV values for both $B^+$ correction methods (Supporting Information Figure S6). No significant difference in the $\mu\text{MTR}_{\text{res}}(\text{APT})$ and $\mu\text{MTR}_{\text{res}}(\text{rNOE})$ values could be found between the MIMOSA FOCUS sequence and the Full CP acquisition with 2-point $B^+$ correction. A significant difference between the $B^+$ correction with $N_{\text{corr}} = 1$ and $N_{\text{corr}} = 2$ can be noted in WM for $\mu\text{MTR}_{\text{res}}(\text{APT})$ of the Full CP sequence ($P = .0236$).

### 3.3 Stability of $B^+$ correction with different $N_{\text{corr}}$

Statistical evaluation of the mean of the contrasts calculated with different numbers of $B^+$ correction points is presented in Figure 8 for 4 measured volunteers. Similar to the results for the sequence comparison, no significant differences between the corrections with $N_{\text{corr}} = 1$ and 2 (minimum $P = .15$) as well as for $N_{\text{corr}} = 1$ and 6 (minimum $P = .42$) could be found. No major differences in the wCoV could be found for the reconstructions with different numbers of measurements for $N_{\text{corr}} = 1, 2, ..., 6$ (Supporting Information Figure S7). Comparison of the 2 contrasts in a representative subject for $N_{\text{corr}} = 0, 1, 2, 6$ shows that small differences between corrections with different numbers of

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**FIGURE 5** $\mu\text{MTR}_{\text{res}}(\text{rNOE})$ (A-F) and $\mu\text{MTR}_{\text{res}}(\text{APT})$(G-L) contrast maps of a single representative volunteer for all 3 sequences acquired with a readout FA = 7°. In contrast to Full CP and MIMOSA CP sequences, no major differences between measurements with $N_{\text{corr}} = 1$ and $N_{\text{corr}} = 2$ can be noted for MIMOSA FOCUS for both $\mu\text{MTR}_{\text{res}}(\text{rNOE})$ and $\mu\text{MTR}_{\text{res}}(\text{APT})$. Inhomogeneities and noisy results close to the cerebellum can be observed for both sequences applying CP readout. Blurring of the contrasts can be observed in the MIMOSA FOCUS sequence and in the central part of the brain of the other 2 sequences.
acquisitions still exist (Supporting Information Figure S8). No major differences of the iCoV of the 2 contrasts for Ncorr = 0, 1...6 could be noted (Supporting Information Figure S9).

3.4 | Repeatability comparison

Because Figure 8 and Supporting Information Figure S8 show no major differences for acquisitions with Ncorr = 1 and 2, the time point repeatability is being investigated only for B1 correction with Ncorr = 1. Figure 9 shows a quantitative evaluation of the time point repeatability based on the 3 measurements performed for 6 different volunteers with MIMOSA FOCUS and B1 correction with Ncorr = 1. No major differences can be observed in the rB1, readout FA, and SNR maps for 3 different measurements in a single volunteer (Supporting Information Figure S10). For μMTRRex(APT) comparable results between volunteers 1, 3, and 4-6 can be noted for both tissues. The MTRRex(rNOE) maps show the best repeatability for volunteer 1 and slightly worse repeatability for the other volunteers for both WM and GM. Overall the CoV for MTRRex(rNOE) reaches a maximum of 2.25%, which shows a good agreement of the repeated measurements for this contrast. Compared to the median of the MTRRex(APT) over all of the measurements, 2 outliers can be noted for volunteer 2. Because of these outliers, the CoV for MTRRex(APT) reaches for this volunteer a value of 7.5%. However, for the other 5 volunteers, the CoVs show a good agreement of the measurements with a maximum CoV of 2.1%.

4 | DISCUSSION

MIMOSA FOCUS shows improved homogeneity of the CEST contrast over the whole-brain compared to the other 2 sequences. In addition, the MIMOSA FOCUS sequence shows fewer artifacts in particular in regions of extremely low rB1 and FA values. The phantom measurements show an overestimation of MTRRex around areas with both extreme high (rB1 > 1.3) and extreme low rB1 (rB1 < 0.5).
that is in agreement with our previous results. The overestimations in MTR$_{Rex}$(APT) in vivo for acquisitions with $N_{corr} = 2$ around areas of extremely low FA and $rB_1$ in Full CP acquisitions are in agreement with results presented by Akbey et al. The sequences applying the CP readout show similar SNR values, as the SNR is mostly dependent on the readout FA. The higher mean FA of the MIMOSA FOCUS sequence results in a broadening of the PSF. The resulting spatial averaging effect leads not only to an increase in the observed SNR, but also to increased image blurring. These observations are in agreement with previous work of Zaiss et al. The increased readout FA of the MIMOSA acquisition does not alter the homogeneity of the acquired MTR$_{Rex}$ contrasts and, therefore, does not bias the comparison of the MIMOSA CP and MIMOSA FOCUS sequences presented in Figure 5. The ringing artifacts in the tSNR maps are most likely based on slight artifacts in the raw images, because these maps are calculated via a pseudo-multiple-replica method that is based on a single acquisition. These artifacts do not appear in the contrast acquisitions as the images used to calculate the contrasts are being normalized with the $M_0$ acquisition. The hemispheric asymmetry of the SNR and tSNR data is most likely caused by an asymmetric positioning of the head in the RF coil.

The statistical evaluations of MTR$_{Rex}$(APT) and MTR$_{Rex}$(rNOE) confirm that these contrasts are influenced by the increased homogeneity of the FA and $rB_1$ distributions. The MIMOSA FOCUS sequence has a smaller spatial variability as both $B_1^+$ correction with $N_{corr} = 1$ and $N_{corr} = 2$ prove to have a noticeably lower inter-subject mean of the wCoV. At the same time opposite to the other 2 sequences MIMOSA FOCUS shows no major differences in between the inter-subject repeatability of the contrasts mean for both investigated contrasts. The $\mu$MTR$_{Rex}$(APT) and $\mu$MTR$_{Rex}$(rNOE) values for Full CP acquisitions with 2-point $B_1^+$ corrections show values that are in agreement with results previously reported. It should be noted, that the $\mu$MTR$_{Rex}$(APT) for Full CP acquisitions shows, in WM, a

**FIGURE 7** Statistically evaluation of the inter-subject repeatability of the $\mu$MTR$_{Rex}$(APT) and $\mu$MTR$_{Rex}$(rNOE) for WM and GM and for different $N_{corr}$. Significant differences between methods are marked with a star for $P < .05$. The MIMOSA FOCUS sequence shows a comparable variation of the results for measurements with 1 and 2 point $B_1^+$ correction. The Full CP measurement shows different variation levels for the 2 tissue types.
significant difference for $B_1^+$ corrections with $N_{corr} = 1$ and $N_{corr} = 2$ points. This is in agreement with previous results by Windschuh et al.\textsuperscript{18} and Akbey et al.\textsuperscript{11}

The stability investigation in vivo shows that with an increasing number of measurements applied during the $B_1^+$ correction the MIMOSA FOCUS sequence still shows some changes in the MTR$\text{R}_{\text{ex}}$ values. However, as can be seen in both Figure 8 and Supporting Information Figure S8, these changes are very small. This is an improvement compared to previous works\textsuperscript{11,18} in which it was shown that full reproducibility of the contrast occurs first with the use of $N_{corr} = 3$. Considering the fact that for $B_1^+$ correction with $N_{corr} = 1$ a maximum iCoV of 4.9% is achieved, and for measurements with 6 points the same value reaches 4% (Figure 8, Supporting Information Figure S9), the additional time effort required for acquisitions can hardly be justified. The results from the sequence comparison in Figure 7 confirm that no significant difference between correction with $N_{corr} = 1$ and $N_{corr} = 2$ exists for the MIMOSA FOCUS sequence. These observations could be contradicted by the results of the phantom study as the results with $N_{corr} = 1$ show a major difference to the results with $N_{corr} = 2$. However, the areas in which major differences occur in the phantom acquisitions correlate with areas of low r$B_1$ values ($rB_1 < 0.5$) of the MIMOSA saturation.

Such areas do not occur in vivo for the MIMOSA saturation technique (Figure 4B,C), and therefore, results with $N_{corr} = 1$ do not show major differences to the results with $N_{corr} = 2$. Hence, the MIMOSA FOCUS sequence can be used together with a single-point $B_1^+$ correction to achieve reproducible results within a total measurement time, including $B_1^+$ mapping (1 min 8 s), of 7 min 22 s. This is an almost 3-fold reduction in measurement time compared to fully reproducible acquisitions with Full CP sequence and 3-point $B_1^+$ correction.\textsuperscript{18}

The linear $B_1^+$ correction was shown to work properly for acquisitions at low $B_1$ amplitudes ($B_1 < 0.5 \mu T$) by Khlebnikov et al.\textsuperscript{17} Our work demonstrates that it also works at higher $B_1$ amplitudes if the variation of the $rB_1$ during the saturation is kept at a sufficiently small level.

For the time point repeatability in the best case, a CoV of 0.5% and 1.1% could be achieved for both MTR$\text{R}_{\text{ex}}(r\text{NOE})$ and MTR$\text{R}_{\text{ex}}(\text{APT})$, respectively. However, it should be noted that higher variations of 7.5% for MTR$\text{R}_{\text{ex}}(\text{APT})$ and 2.25% for MTR$\text{R}_{\text{ex}}(r\text{NOE})$ were also observed. The overall higher CoV value of the MTR$\text{R}_{\text{ex}}(\text{APT})$ contrast could be linked to a lower SNR of the APT in comparison to the rNOE effect. The observed CoV in $\mu$MTR$\text{R}_{\text{ex}}(r\text{NOE})$ is much smaller than the variation between different scanner systems reported by Voelker et al.\textsuperscript{44} Unfortunately, the exact causes for the
2 outlier measurements of volunteer 2 could not be clearly identified. Because an increased value of $MTR_{\text{Rex}}(\text{NOE})$ and $MTR_{\text{Rex}}(\text{APT})$ is visible in both tissue types, it could indicate a change in the effective amplitude of the saturation train. This could be potentially caused by a variation in the transmitter voltage adjustments. However, as this variation was very small (~3%), it does not provide enough evidence to conclude that this is the only or main reason. Another potential cause for a change in the effective amplitude is the subject movement and change of position after transmitter adjustments or during the acquisition.45 This is especially important in case of patient studies where strong motion of the patient could occur, and potentially decrease the repeatability even further. Potential mitigation of this effect could be achieved in the future with prospective motion correction methods.46 Another potential issue could be variations in the optimization of the FOCUS pulses. However, the results in Supporting Information Figure S10 indicate that even though very small changes occur in the resulting FA distribution they have negligible influence on the resulting SNR. Therefore, no relevant influence on the $MTR_{\text{Rex}}$ contrasts because of the FOCUS optimization is expected. Because it was not possible to define the exact reasons for the occurrence of the outliers, it is important to consider that a variation of $MTR_{\text{Rex}}(\text{APT})$ of at least 8% could occur for this sequence.

Until now, the repeatability of $B_1^+$ corrected quantitative CEST acquisitions in the brain at ultra-high field was not investigated. For 3T acquisitions, inter-subject repeatability of CEST sequences with different reconstruction methods was investigated by Msayib et al.47 Repeatability of APTw CEST acquisitions were also investigated by Lee et al.48 Mueller et al.14 reported results for a similar approach of whole-brain snapshot CEST using, however, 3D-EPI at 3T. Msyaib et al.47 noted that no major differences were observed between time point and inter-subject repeatability. Lee et al.48 reported an intersession repeatability of 21%. For MIMOSA FOCUS with single-point $B_1^+$ correction ($N_{\text{corr}} = 1$) our maximal time point repeatability is higher for $MTR_{\text{Rex}}(\text{APT})$ (maximal CoV in WM = 7.5% in GM = 4.5%, c.f. Figure 9D) than the inter-subject repeatability (iCoV = 2.4% in WM and 2.3% in GM) results presented in Figure 7. Our iCoV of MIMOSA FOCUS is much smaller than the iCoV for $MTR_{\text{Rex}}(\text{APT})$
correction is necessary if the rB1 value during contrast and is in agreement with our previous results\textsuperscript{43} and compressed. This change of the Z-spectrum affects the final magnetization's steady state and as a result, the Z-spectrum is being during the measurements. This change influences the magnetization and is in agreement with our previous results\textsuperscript{43} and with results presented by Zaiss et al.\textsuperscript{9}

In phantom measurements, the MTR\textsubscript{Res}(rNOE) values for MIMOSA FOCUS are slightly lower than in the MIMOSA CP sequence. This effect could be traced back to a change of the T1 value because of a temperature change of the phantom during the measurements. This change influences the magnetization’s steady state and as a result, the Z-spectrum is being compressed. This change of the Z-spectrum affects the final contrast and is in agreement with our previous results\textsuperscript{43} and with results presented by Zaiss et al.\textsuperscript{9}

Our sequence presented in this study has a lower nominal resolution (2.5 mm isotropic) than the WB snapshot EPI sequence presented by Akbey et al\textsuperscript{11} (2.0 mm isotropic). However, it should be possible to transfer the presented methods into a WB-EPI sequence. Additionally, higher nominal resolutions for WB measurements with the use of a GRE-based sequence should be possible with the use of compressed sensing methods, as it was previously shown for EPI and fast spin-echo sequences.\textsuperscript{49,50} The MIMOSA FOCUS sequence does not show artifacts in areas in which previous methods did\textsuperscript{11} and as such our method proves to be overall more robust.

In the future, the B\textsubscript{1} correction for whole-brain measurements could potentially be omitted if further increase in homogeneity of the saturation is achieved. A potential solution for this would be the introduction of additional optimization of the 2 modes applied in MIMOSA to achieve a more uniform saturation transfer. Another potential approach would be the application of different transmit SENSE solutions such as presented by Tse et al\textsuperscript{20} or Cao et al.\textsuperscript{22} However, it should be noted that our phantom results clearly indicate that a multi-point B\textsubscript{1} correction is necessary if the rB\textsubscript{1} value during saturation drops below 0.5. Further performance improvement could be obtained by optimizing the FOCUS pulses for the brain region rather than for the entire head only. Such a solution could further increase the homogeneity of the read-out and the homogeneity of the SNR.

5 | CONCLUSION

A combination of snapshot GRE CEST with 2 pTx methods was implemented and analyzed. This new sequence, called MIMOSA FOCUS, together with a simple linear B\textsubscript{1} correction method, allows for quantitative CEST measurements in the whole-brain. A worst case CoV of 7.5% for time point repeatability for MIMOSA FOCUS was obtained. The MIMOSA FOCUS sequence proves to be a robust and fast method, which could be successfully applied for whole-brain quantitative CEST measurements with an acquisition time of just 7 min 22 s.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION
Additional Supporting Information may be found online in the Supporting Information section.

FIGURE S1 Simulations of the PSF in 1st and 2nd phase-encoding (PE) direction for WM and GM with different FA values. The 1st PE direction shows a broader PSF than the 2nd PE direction due to a higher number of acquisitions and higher GRAPPA factor in this direction. A broadening of the PSF can be noted in both PE directions with the increase of the FA.

FIGURE S2 Simulated rFWHM of the PSF of WM, GM and cerebrospinal fluid (CSF) in dependency from FA in the two different PE directions for FA values as well as the mean value of these two directions between 1 and 15 degrees. The Ernst Angle is marked for WM. An increase of the rFWHM can be noted with the increase of the FA. Around the Ernst angle the value stays more constant than for increased FA values. These results are very similar to the results of Zaiss et al.

FIGURE S3 Simulated mean rFWHM of the PSF relative to the mean rFWHM of FA = 5° (A-C) and measured SNR (D-F) for a single volunteer. The simulation of the rFWHM was based on the FA maps and tissue segmentations of one measurement with the MIMOSA CP sequence with a FA = 7° (A) and two measurements with MIMOSA FOCUS with two different FA = 5°, 7° (B and C). The CP mode simulations show a major increase of the relative FWHM of the PSF (rFWHM) in the central part of the brain. This increase of the PSF radius is comparable or slightly higher than the increase of the PSF radius in the simulations with the FOCUS pulse and FA of 7°. Overall, the FOCUS pulse has a more homogeneous distribution of the PSF radius. The spatial distribution of the simulated rFWHM does not coincide with the spatial distribution of the measured SNR, since the receiver coil profiles also influence the SNR. The mean acquired SNR shows a comparable increase as the mean increase of the PSF for the acquisitions with 7° compared to an acquisition with 5°. This indicates that the increase of the SNR is mainly the result of increased spatial averaging due to the increased rFWHM of the PSF.

FIGURE S4 MTR_{Res} (rNOE) and MTR_{Res} (APT) contrasts and SNR and tSNR values for measurements with MIMOSA FOCUS in a single volunteer with 3 different FA = 5°, 7° and 9°. An increase in blurriness due to an increase in PSF can be noticed with the increase of the FA. An increase in the SNR and tSNR can also be observed with the increase of the FA.

FIGURE S5 MTR_{Res} (rNOE) and MTR_{Res} (APT) contrasts and SNR and tSNR values for one measurement with MIMOSA CP sequence with a FA = 7° and two measurements with MIMOSA FOCUS with 2 different FA = 5°, 7° for a single volunteer. For the MIMOSA FOCUS sequence, a single-point B_{1+} correction was performed and for the MIMOSA CP sequence a two-point B_{1+} correction was applied. An increase in blurriness due to an increase in PSF can be noticed with the increase of the FA. A comparable SNR and tSNR can be observed for the measurements with MIMOSA CP and MIMOSA FOCUS with the use of FA = 5°.

FIGURE S6 iCoV of µMTR_{Res} (rNOE) and µMTR_{Res} (APT) in WM and GM for measurements with Full CP, MIMOSA CP and MIMOSA FOCUS and B_{1+} correction with different N_{corr}. Measurements with MIMOSA FOCUS show the smallest differences in iCoV between measurements with N_{corr} = 1 and N_{corr} = 2.

FIGURE S7 Statistical evaluation of the wCoV for MTR_{Res} (rNOE) and MTR_{Res} (APT) in WM and GM for measurements with MIMOSA FOCUS and B_{1+} correction with different N_{corr}.
FIGURE S8 Comparison of MTRrex(rNOE) (top row) and MTRrex(APT) (bottom row) for MIMOSA FOCUS without B1+ correction (1st column) and with B1+ correction with Ncorr = 1, 2 and 6 for a different subject than in Figures 3 and 4. The uncorrected contrasts show lower MTRrex(APT) and MTRrex(rNOE) values in the cranial part of the brain and in the cerebellum. All three presented correction methods correct for this inhomogeneity and no major differences between these three methods can be observed.

FIGURE S9 iCoV of the μMTRrex(APT) and μMTRrex(rNOE) in WM and GM for measurements with MIMOSA FOCUS and B1+ correction with different Ncorr. A maximum iCoV of 4.9% can be observed for Ncorr = 1 for μMTRrex(APT) in WM. The biggest difference in iCoV (1.2%) between Ncorr = 1 and Ncorr = 6 occurs for μMTRrex(APT) in GM.

FIGURE S10 Comparison of Saturation rB1, Readout FA and SNR for a single volunteer measured 3 times with the MIMOSA FOCUS sequence. No major differences in the distribution of the rB1, FA and SNR can be noted between the different measurements.

TABLE S1 Fitting parameters of the Lorentzian functions, amplitude (A), width (G in ppm) and peak position (ω in ppm) used to acquire reference and label spectrum. Presented are parameters for Water (1), Amide (2), rNOE (3), Semi-solid Magnetic Transfer (4) and Amine (5) peaks.

TABLE S2 Evaluation of the mean, standard deviation and CoV of rB1, FA, SNR and MTRrex(rNOE) and MTRrex(APT) over the phantom regions where the rB1 of MIMOSA is over 0.6, for the three compared methods. An increase of the readout μFA can be observed for the MIMOSA FOCUS sequence. The MIMOSA CP and MIMOSA FOCUS sequence show a decreased CoV of rB1. In general, a decrease of the mean CoV of the contrasts can be observed for the MIMOSA FOCUS and MIMOSA CP sequence. Additionally, the MIMOSA FOCUS sequence shows a comparable CoV of approx. 14% for both MTRrex(rNOE) and MTRrex(APT) and with both Ncorr = 1 and Ncorr = 2. In contrast, the MIMOSA CP sequence shows a different CoV value for both MTRrex(rNOE) and MTRrex(APT) between the different Ncorr numbers. This indicates that overall the MIMOSA FOCUS sequence is more stable than the MIMOSA CP sequence.

TABLE S3 Evaluation of the tSNR for the three compared methods in case of the three measured volunteers. Overall an increase of the tSNR can be observed in case of the MIMOSA FOCUS sequence. This increase is mainly caused by the higher mean readout FA of the MIMOSA FOCUS sequence and the resulting from it increase of the PSF. (Supporting Information Tables S5-6 and Supporting Information Figures S1-S3)

TABLE S4 Evaluation of the normalized root mean square error of the three pTx methods in the whole phantom and in phantom regions with rB1,MIMOSA > 0.6. Additionally the μ±σ of the FA NRMSE over the whole brain across 13 Volunteers for the three methods is presented. NRMSE was calculated as NRMSE = \sqrt{\frac{\sum_{i=1}^{N} (FA - 7)^2}{N}} / 7, as the nominal FA of the readout is 7°. The NRMSE of the FOCUS pulse is much lower than the NRMSE of the CP mode. A reduction of the NRMSE can be observed for the MIMOSA method in comparison to the CP mode in all cases.

TABLE S5 Quantitative evaluation in form of μ ± σ and wCoV MTRrex contrasts in different tissue types and of the readout FA, SNR and tSNR values for whole brain for measurements with MIMOSA FOCUS with three different readout FA = 5°, 7° and 9° for a single volunteer. Overall the achieved wCoV values for this volunteer were slightly smaller for the MTRrex(APT) contrast and comparable for the MTRrex(rNOE) contrast than the mean reported in Figure 6.

TABLE S6 Quantitative evaluation in form of μ±σ and wCoV of the readout FA, SNR and tSNR values for one measurement with MIMOSA CP sequence with a FA = 7° and two measurements with MIMOSA FOCUS with 2 different FA = 5°, 7° for a single volunteer over the WB. A decrease of the wCoV of the FA and SNR can be observed in case of the use of the FOCUS pulse during readout.

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