Hybrid $B_1^+$-shimming and gradient adaptions for improved pseudo-continuous arterial spin labeling at 7 Tesla

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Purpose: To improve pseudo-continuous arterial spin labeling (pcASL) at 7T by exploiting a hybrid homogeneity- and efficiency-optimized $B_1^+$-shim with adapted gradient strength as well as background suppression.

Methods: The following three experiments were performed at 7T, each employing five volunteers: (1) A hybrid (ie, homogeneity-efficiency optimized) $B_1^+$-shim was introduced and evaluated for variable-rate selective excitation pcASL labeling. Therefore, $B_1^+$-maps in the V3 segment and time-of-flight images were acquired to identify the feeding arteries. For validation, a gradient-echo sequence was applied in circular polarized (CP) mode and with the hybrid $B_1^+$-shim. Additionally, the gray matter (temporal) signal-to-noise ratio (tSNR) in pcASL perfusion images was evaluated. (2) Bloch simulations for the pcASL labeling were conducted and validated experimentally, with a focus on the slice-selective gradients. (3) Background suppression was added to the $B_1^+$-shimmed, gradient-adapted 7T sequence and this was then compared to a matched sequence at 3T.

Results: The $B_1^+$-shim improved the signal within the labeling plane (23.6%) and the SNR/tSNR increased (+11%/-11%) compared to its value in CP mode; however, the increase was not significant. In accordance with the simulations, the adapted gradients increased the tSNR (35%) and SNR (45%) significantly. Background suppression further improved the perfusion images at 7T, and this protocol performed as well as a resolution-matched protocol at 3T.

Conclusion: The combination of the proposed hybrid $B_1^+$-phase-shim with the adapted slice-selective gradients and background suppression shows great potential for improved pcASL labeling under suboptimal $B_1^+$ conditions at 7T.
1 | INTRODUCTION

Arterial spin labeling (ASL) is an MRI technique used to measure perfusion without intravenous contrast agents.\(^1,2\) Thus, it offers the possibility of a non-invasive brain perfusion examination, which is particularly important when contrast agents are contraindicated (eg, due to renal insufficiency).\(^3\)

ASL is based on the inversion of blood magnetization by radiofrequency (RF) pulses. Subsequently, the inverted blood can be used as an endogenous tracer. After a certain delay, the tagged blood enters the region to be examined and a labeled image is acquired. Additionally, a control image is acquired without the prior inversion of the blood magnetization. The difference of these two images is denoted as the perfusion-weighted image.\(^1,2\)

In general, ASL suffers from a relatively low signal-to-noise ratio (SNR). ASL benefits two-fold from higher magnetic field strength, both due to an overall higher SNR\(^4-7\) and an increased longitudinal relaxation time (\(T_1\)).\(^7,8\) Hence, increasing the field strength leads to improvements in ASL images, as has already been observed at 3T in comparison to 1.5T. ASL results are expected to improve further through the use of ultra-high magnetic field (UHF) strengths (\(B_0 \geq 7T\)).\(^9\)

However, the implementation of pseudo-continuous ASL (pcASL)\(^10\) at UHF holds challenges, such as an increased \(B_1^+\) and \(B_0\)-inhomogeneity as well as a higher specific absorption rate (SAR). To overcome SAR restrictions at 7T, variable-rate selective excitation (VERSE) has been used for various MRI applications\(^11-13\) and also seems to be a highly promising technique for pcASL.\(^14,15\) To counteract \(B_1^+\)-inhomogeneity, several suggestions have been made, such as the inclusion of dielectric pads to improve \(B_1^+\) efficiency,\(^16,18\) additional neck coils for labeling,\(^19\) or positioning the labeling plane through the motor cortex.\(^20\) However, all of these solutions either require hardware changes or impair image coverage. Tong et al\(^15\) suggested that \(B_1^+\) amplitude and phase shimming for the labeling pulses could be used in combination with VERSE, which performed equally with truncated pcASL flip angles at 3T.\(^15\) In contrast to an amplitude and phase shim, a phase-only shim is easier to implement and avoids having one channel distribute most of the total RF power.\(^7,21\)

Regarding the pcASL labeling train itself, higher slice-selective gradients (\(G_{\text{max}}\)) lead to narrower labeling slices. Thus, an orthogonal blood flow to the labeling slice is more likely due to the fact that the influence of small vessel bends in the labeling area can be reduced. Narrow labeling slices are also recommended by the International Society for Magnetic Resonance in Medicine (ISMRM) perfusion study group and European consortium for ASL in dementia.\(^22\) However, low \(B_1^+\) and, consequently, insufficient labeling flip angles lead to suboptimal inversion. On the contrary, with thicker labeling slices and lower maximum gradients, the labeling should benefit from longer exposure to the pcASL train.

In this work, we propose an optimized, hybrid \(B_1^+\)-phase-shim solution trading transmission homogeneity and efficiency combined with VERSE pulses and examine the impact of slice-selective gradients of the pcASL labeling train. Furthermore, we add background suppression (BS) pulses at 7T and compare the \(B_1^+\)-shimmed, gradient-adapted pcASL sequence to a matched sequence at 3T.

2 | METHODS

All measurements were performed on a 7T MR system (MAGNETOM Terra, Siemens Healthcare GmbH, Erlangen, Germany) using a 32-channel Rx/8Tx head coil (Nova Medical, Wilmington, Massachusetts, USA) and a 3T MR system (MAGNETOM Prisma, Siemens Healthcare GmbH, Erlangen, Germany) employing a 64-channel Rx head coil (Siemens Healthcare GmbH, Erlangen, Germany) as well as a body coil for transmission. The measurements were carried out in accordance with institutional guidelines and with approval from the local ethics committee (Friedrich-Alexander University [FAU], Erlangen-Nürnberg, Germany). For \(B_1^+\) calibration, a vendor provided reference scan routine consisting of a fast saturation recovery turbo flash \(B_1^+\) mapping sequence\(^23\) in three transversal slices was used. Thus, the transmitter voltage was set such that the upper 20th percentile of the flip angles reached at least the nominal value.

The pcASL sequences for all measurements consisted of an unbalanced labeling scheme with Hanning window-shaped pulses.\(^10\) For the readout, a vendor provided 2D gradient echo planar imaging (EPI) sequence was used. The respective sequence parameters for 3T and 7T can be found in Table 1. All pcASL labeling pulses at 7T were modified using the VERSE algorithm\(^11,13,24\) with a maximum amplitude reduction factor of 2 and a maximum VERSE gradient of 10 mT/m.

Prior to all pcASL measurements, a head/neck time-of-flight (TOF) sequence was applied to identify the main feeding vessels of the brain: the right/left internal carotid artery and right/left vertebral artery. The labeling plane was located within the V3 segment for all scans at 3T and 7T due to limited coil coverage at 7T (Figure 1A). Additional anatomical data were acquired in all MRI sessions using a \(T_1\)-weighted sequence (magnetization prepared rapid gradient echo)\(^25,26\).
TABLE 1  Main sequence parameters used at 7T and 3T for all three experiments

| Parameter                              | 7T               | 3T               | 3T               |
|----------------------------------------|------------------|------------------|------------------|
| pcASL                                  | 534-591*         | 500              | 500              |
| Pulse duration [µs]                    | 534-591*         | 500              | 500              |
| Pulse separation [µs]                  | 500              | 500              | 500              |
| Target average $B_1^+$ [µT]            | 1.5              | 1.5              | 1.5              |
| VERSE reduction factor                 | 2                | –                | –                |
| Max. VERSE gradient [mT/m]             | 10               | –                | –                |
| Labeling duration [ms]                 | 1500             | 1500             | 1500             |
| Post labeling delay [ms]               | 1800             | 1800             | 1800             |
| TS Presaturation [ms]                  | 5000             | 5000             | 5000             |
| TI slice-sel. BS [ms]**                | 4979             | 4431             | 4431             |
| TI non.-sel. BS [ms]**                 | 1790             | 1358             | 1358             |
| Efficiency slice-sel. BS**             | 0.976            | 0.999            | 0.999            |
| Efficiency non.-sel. BS**              | 0.912***         | 0.997            | 0.997            |
| EPI                                    |                  |                  |                  |
| Voxel size [mm$^3$]                    | 2 × 2 × 4        | 2 × 2 × 4        | 3.5 × 3.5 × 4    |
| Matrix size                            | 116 × 116        | 116 × 116        | 66 × 66          |
| Partial Fourier                        | 6/8              | 6/8              | –                |
| GRAPPA factor                          | 2                | 2                | 2                |
| TE [ms]                                | 15               | 15               | 15               |
| Flip angle [°]                         | 90               | 90               | 90               |
| Bandwidth [Hz/px]                      | 2052             | 2052             | 1942             |
| Number of slices                       | 15               | 15               | 15               |
| Repetitions (labeling/control pairs)   | 36 (18)          | 54 (27)          | 36 (18)          |

*The Variable-Rate Selective Excitation (VERSE) pulse duration differs due to different maximum gradients and slew rate limitations; **The inversion pulses for background suppression (BS) were only used in experiment 3; ***At 7T, the voltage of the non-selective adiabatic background suppression pulses was reduced to 60% of the initial voltage.

**FIGURE 1**  A, TOF MIP and position of the labeling plane (yellow). The maximum thickness of the labeling slice in the V3 segment is denoted by the blue arrow. B, $B_1^+$-phase-shimming routine: A $B_1^+$ map and a TOF (left) were acquired and thin MIPs were generated with the TOF data. In these MIPs, the four main feeding arteries were identified and two masks were created around them (green area). The masks were transferred to the $B_1^+$ maps to shim within these ROIs. The lower row images show the $B_1^+$ maps (at 82 V, reference voltage = 269 V): left in CP mode, right after $B_1^+$-shimming. The upper row shows the $B_1^+$ efficiency maps scaled from 0 to 1.
for the segmentation of gray matter, white matter, and cerebrospinal fluid.

Data analysis of the pcASL sequences was performed using SPM12 (Wellcome Trust Centre for Neuroimaging),\textsuperscript{27} Matlab2017b (MathWorks) and the FMRIB Software Library (FSL)\textsuperscript{28}: (1) Images were realigned, (2) coregistered to the structural image, (3) perfusion images were calculated. The pcASL perfusion data were scaled voxel-wise using proton-density-weighted M\textsubscript{0} images. These images were acquired with the same readout, however, no pcASL RF pulses (only gradients) were applied and the TR was prolonged to 10 s. For the calculation of the cerebral blood flow (CBF), a method proposed by Buxton et al\textsuperscript{29} was applied to the M\textsubscript{0}-calibrated perfusion images. The T\textsubscript{1} of blood was assumed to be 1664 ms at 3T\textsuperscript{30} and 2587 ms at 7T.\textsuperscript{31} The pcASL labeling efficiency was determined via a Bloch simulation for each volunteer with an assumed mean blood velocity of 40 cm/s and off-resonances based on double-echo B\textsubscript{0} maps. For the inversion efficiency of the adiabatic background suppression pulses, additional Bloch simulations were obtained (compare Table 1) and the labeling efficiency was corrected globally.\textsuperscript{31} Additionally, the perfusion images were distortion corrected using the Topup toolbox.\textsuperscript{32-34} Therefore, two M\textsubscript{0} images were acquired with reversed phase-encode blips. Using this pair, the susceptibility-induced off-resonance field was estimated via the Topup toolbox.\textsuperscript{32,33} This field map was used to unwarped the perfusion and CBF images.

Voxel-wise temporal SNR (tSNR) in the gray matter was calculated as the mean perfusion signal divided by its SD across all measurements, excluding the first and last slices due to possible motion correction errors. Furthermore, spatial SNR in the gray matter was estimated for all slices except the first and last slices. Therefore, the even- and odd-numbered image time points of the perfusion-weighted time-series were averaged separately. To estimate the SNR, the mean value of the gray matter in the sum of these two images was divided by the SD across the gray matter in the difference image.\textsuperscript{35,36} Additionally, the tSNR and SNR efficiencies were calculated with \( \text{tSNR} / \sqrt{N_{\text{Rep}} \cdot TR} \), where \( N_{\text{Rep}} \) denotes the number of repetitions.\textsuperscript{37}

In total, three pcASL experiments were conducted: (1) At 7T, two different labeling pulses were compared: (i) a phase-shimmed labeling pulse with a trade-off in transmission efficiency and homogeneity and (ii) a circular polarized (CP) mode. The same maximum gradient (\( G_{\text{max}} \)) and average gradient (\( G_{\text{ave}} \)) were used in both cases, as recommended for 3T by Zhao et al.\textsuperscript{38} (2) Bloch simulations of the labeling pulses and their experimental evaluations were performed at 7T. (3) A comparison with regard to tSNR/SNR was carried out between 7T, with and without background suppression, and 3T with background suppression.\textsuperscript{39} For all experiments, the readout pulses were obtained in CP mode.

Statistical analyses were carried out via paired t-tests for all subject-to-subject comparisons and via an analysis of variance (ANOVA) test, followed by a Bonferroni corrected multiple comparison test (significance level \( P < .05 \), for the 7T and 3T multiple comparisons.

### 2.1 Experiment 1: \( B_1^+ \)-phase-shimming for pcASL labeling compared to CP mode at 7T

To calculate the \( B_1^+ \)-phase-shim sets, 2D \( B_1^+ \) maps were acquired at the labeling location using a vendor-provided interferometric-magnetization-prepared saturation recovery turbo gradient echo sequence without flow compensation.\textsuperscript{23} The scan was followed by a TOF in the same location (Supporting Information Table S1), and maximum intensity projections (MIPs) were generated to identify the four feeding arteries in the V3 segment. Masks for the left and right feeding arteries were generated manually (Figure 1B). Within these two regions of interest (ROIs), \( B_1^+ \)-phase-shimming was performed by minimizing:

\[
\text{cost} = (1 - \lambda) \cdot \text{CoV}^2 + \lambda \cdot \eta^{-2},
\]

where \( \lambda \) is the regularization factor (fixed at 0.3), \( \text{CoV} \) is the coefficient of variation defined by\textsuperscript{21,40,41}:

\[
\text{CoV} = \frac{\text{std} \left( \sum_{c=1}^{C} B_{1,c}^+ (r) \right)}{\text{mean} \left( \sum_{c=1}^{C} B_{1,c}^+ (r) \right)}
\]

and \( \eta \) is the mean \( B_1^+ \) efficiency\textsuperscript{21,42,43}:

\[
\eta = \frac{\text{mean} \left( \sum_{c=1}^{C} B_{1,c}^+ (r) \right)}{\sum_{c=1}^{C} \left| B_{1,c}^+ (r) \right|}.
\]

The \( B_1^+ \)-shim optimization, including artery identification, was performed online using a Matlab2017b runtime. First, the calculated \( B_1^+ \)-shim set was applied to the excitation pulse of a flow-compensated gradient echo (GRE) sequence (repetition time [TR] = 18 ms, echo time [TE] = 3.57 ms, nominal flip angle = 5°, interpolated to 0.4 x 0.4 x 1 mm\textsuperscript{3}, slices = 20, acquisition time [TA] = 32 s) for a direct examination of the shim. This sequence was acquired at the labeling location and the resulting signal was compared to the CP mode acquisition for all four feeding arteries. Subsequently, the shim set was applied to the entire VERSE pcASL pulse train and the resulting tSNR/SNR value was compared to the value obtained by CP mode excitation. Here, the maximum (average) gradient amplitude of the pcASL pulses was set to 3.5 mT/m (0.5 mT/m), as recommended in Ref. [38], to minimize the influences of \( B_0 \) inhomogeneity and pulsatile flow.
The signals in the arteries as well as the pcASL sequences using $B^+_{1}$-shimming were compared to CP mode in five healthy volunteers (mean age: 24.8 ± 1.2). The pcASL measurements were performed twice using an interleaved scheme (CP, hybrid $B^+_{1}$-shim, CP, hybrid $B^+_{1}$-shim) with 36 repetitions each (18 labeling/control pairs, Table 1), and evaluated via the mean tSNR and SNR values. No inversion pulses for background suppression were applied to lower the SAR, avoiding longer repetition times and, consequently, prolonged scan times. However, two pre-saturation pulses were used. The TR of the sequences was set to the minimum value for each volunteer according to the constraints imposed by the SAR (TR range: 6600-8500 ms), yielding a mean TA of $\overline{TA} = 5:07$ min.

### 2.2 Experiment 2: Gradient adaption for the pcASL labeling

To investigate the impact of low $B^+_{1}$ amplitudes, Bloch simulations were performed. Therefore, the labeling train was simulated as performed by the MRI scanner using different $B^+_{1}$ amplitudes (0.8:0.1:3.6 µT) for the labeling pulses and different $G_{\text{max}}$ values (2.8:0.7:7.0 mT/m) at a mean blood velocity of 40 cm/s. $G_{\text{ave}}$ was kept fixed to the proposed ratio of $G_{\text{ave}} = \frac{1}{7} G_{\text{max}}$.

To examine the simulation results, five volunteers (mean age: 25.6 ± 2.1) were measured with the optimum feasible $G_{\text{max}}$ according to the simulation (constrained by the individual, straight segments of the arteries; see Figures 1A and 3) in the following referred to as adapted gradient. Moreover, the thinnest feasible labeling layer was used, as recommended in Ref. [22], thus serving as the clinical gold standard. Due to VERSE, $G_{\text{max}} = 7$ mT/m was the maximum achievable gradient strength for the applied pcASL labeling. The previously examined hybrid $B^+_{1}$-phase-shimming for the labeling plane was applied in all acquisitions for this experiment. The measurements were conducted twice in an interleaved scheme, as described above for experiment 1 (36 repetitions each: 18 labeling/control pairs, Table 1) and the mean tSNR/SNR was obtained. As in the first experiment, no inversion pulses for background suppression were used and the TR was set to fulfill the SAR limit ($\overline{TA} = 5:08$ min).

### 2.3 Experiment 3: Influence of inversion pulses for BS at 7T and comparison of 3T and 7T

In this experiment, 7T pcASL with VERSE, a hybrid $B^+_{1}$-shim and individually adapted $G_{\text{max}}$ values was examined without and with hyperbolic-secant adiabatic inversion pulses: one slice-selective inversion pulse before the labeling pulse train and one non-selective inversion pulse afterwards. The amplitudes of the non-selective inversion pulses at 7T were limited to 60% of the vendor-suggested voltage to reduce the SAR. Inversion pulse timings were calculated as suggested in Ref. [39] (see Table 1). The protocol containing the inversion pulses for BS was further compared to conventional pcASL at 3T with matched gradients as well as inversion pulses for BS (timings calculated as for 7T, see Table 1) for every volunteer. No VERSE was used at 3T. Again, five volunteers (mean age: 26.0 ± 2.5) were measured in both MRI scanners. In total, two MRI scans were performed at 3T with a minimum, fixed TR. One with the same resolution as at 7T (3T $2 \times 2 \times 4$) but featured 54 repetitions (27 labeling/control pairs), leading to approximately the same TA as that for 7T ($\overline{TA}_{3T} = 5:42$ min). The second measurement ($3T_{3.5} \times 3.5 \times 4$) used a lower resolution ($3.5 \times 3.5 \times 4$ mm$^3$), $\overline{TR}_{3T} = 5700$ ms, $\overline{TA}_{3T} = 3:50$ min), reflecting the expected intrinsic SNR gain of 3.14 from 3T to 7T. Here, only one measurement was performed at each field strength (7T: 36 repetitions, $3T_{2} \times 2 \times 4$: 54 repetitions, $3T_{3.5} \times 3.5 \times 4$: 36 repetitions). The tSNR/SNR and background suppression were then evaluated. As in the previous experiments, the TR at 7T was kept as short as the SAR constraints allowed (TR: 8400 ms to 9400 ms), resulting in $\overline{TA} = 6:02$ min.

### 3 RESULTS

#### 3.1 Experiment 1: $B^+_{1}$-phase-shimming for pcASL labeling compared to CP mode at 7T

Figure 2A shows the average GRE signal intensity in the four feeding arteries in CP mode and $B^+_{1}$-shim mode. Each colored line represents one volunteer. Using the hybrid $B^+_{1}$-shim, the signal in the arteries significantly ($P = .0002$) increased by 23.6 ± 4% compared to the signal in CP mode, reflecting the increased means of the $B^+_{1}$ amplitudes within the optimization ROIs, which show a gain of 18.5 ± 5% ($P = .003$) (cf. Figure 2B). The resulting means of tSNR and SNR when applying the same shim sets to the labeling of the pcASL sequence are presented in Figure 2B,C. The mean tSNR over all volunteers using $B^+_{1}$-shimming was 0.61 ± 0.14, while in CP mode, it was 0.55 ± 0.2, resulting in an average non-significant increase of 11%. However, no tSNR gain through $B^+_{1}$-shimming was observed above a certain level (tSNR$_{CP} > 0.7$, Volunteers 1 and 2). The mean gray matter SNR also showed a non-significant average increase of 11% for the $B^+_{1}$-shim mode compared to the CP mode (SNR = 1.99 ± 0.63/ 1.79 ± 0.95, respectively). The tSNR and SNR efficiencies in CP mode were 0.033 ± 0.013 and 0.110 ± 0.061,
respectively. $B_i^+$-shimming of the labeling slice resulted in tSNR and SNR efficiencies of $0.037 \pm 0.010$ and $0.122 \pm 0.043$, respectively.

According to the optimization, a $B_i^+$ amplitude improvement of $18.6 \pm 5.6\%$ could be reached for the hybrid shim compared to the CP mode. However, due to SAR constraints and the limited 7T head coil coverage, the required $B_i^+$ amplitude ($3.6 \mu T$) could not be reached, resulting in an average mean $B_i^+$ of $0.8 \pm 0.1 \mu T$ for all five volunteers.

### 3.2 Experiment 2: gradient adaption for the pcASL labeling

The Bloch simulations show an increased labeling efficiency with lower $G_{\text{max}}$ values at suboptimal $B_i^+$ amplitudes (Figure 3A). Nonetheless, for lower $G_{\text{max}}$ values, the slice thickness increases (Figure 3B). Since the labeling plane was located in the V3 segment, the slice thickness was restricted by the distances between the bends in the vessels (Figure 1A). Hence,
the slice thickness was set to the full width at log(2) of the normalized magnetization of the simulated slice profile (dotted line in Figure 3B).

The simulation results were validated by evaluating the tSNR and SNR, measured with the individually adapted gradients (four volunteers: 3.5 mT/m, one volunteer: 4.2 mT/m, straight vessel length in the V3 segment: 1.48 ± 0.18 cm) compared to \( G_{\text{max}} = 7 \) mT/m. For all five subjects, the individually adapted maximum gradient resulted in significantly higher tSNR (\( p = .03 \)) and SNR (\( p = .02 \)) compared to \( G_{\text{max}} = 7 \) mT/m (Figure 4A,B). The mean tSNR with \( G_{\text{max}} = 7 \) mT/m was 0.42 ± 0.06 compared to 0.58 ± 0.13 for the individually adapted gradient, leading to an average gain of 35%. The SNR evaluation showed an increase of 45% from \( G_{\text{max}} = 7 \) mT/m (SNR = 1.37 ± 0.29) to the individually adapted gradients (SNR = 1.99 ± 0.63). According to the simulations, the labeling efficiency increased for these volunteers, going from 0.56 ± 0.07 with \( G_{\text{max}} = 7 \) mT/m to 0.76 ± 0.06 with the individually adapted \( G_{\text{max}} \). The tSNR/ SNR efficiencies reflect those values, as they are 0.026 ± 0.005/0.083 ± 0.020 and 0.035 ± 0.010/0.122 ± 0.043 for \( G_{\text{max}} = 7 \) mT/m and the adapted gradient, respectively. An example of the perfusion signal for the individually adapted \( G_{\text{max}} \) compared to 7 mT/m is illustrated in Figure 5.

### 3.3 | Experiment 3: Influence of Inversion Pulses for BS at 7T and Comparison of 3T and 7T

Figure 6A,B show the comparison of tSNR and SNR for 7T measurements with and without inversion pulses for background suppression. The tSNR and SNR showed significant increases (\( p_{\text{tSNR}} = 0.012, p_{\text{SNR}} = 0.019 \)) with the addition of inversion pulses by an average of 50.1% and 75.1%, respectively. These increases could also be shown in terms of tSNR/SNR efficiency: without inversion pulses, the efficiency was 0.028 ± 0.01/0.091 ± 0.037, whereas, with inversion pulses, it was 0.041 ± 0.014/0.158 ± 0.067.

Figure 6C shows the tSNR for the 7T results (two volunteers: 3.5 mT/m, three volunteers: 4.2 mT/m) compared to the matched sequence 3T \( \times 2 \times 2 \times 4 \) and lower-resolution sequence 3T \( \times 3.5 \times 3.5 \times 4 \) results. According to the tSNR, the 7T measurements performed as well as (non-significant difference, \( p > .05 \)) the matched 3T sequence, with a relative average tSNR for 7T compared to 3T of 1.04. The low-resolution 3T protocol showed a significantly increased average tSNR of 72.7% (\( p = .006 \)) compared to 3T \( \times 2 \times 2 \times 4 \) and of 74% (\( p = .01 \)) compared to the 7T sequence. In terms of the tSNR efficiency, the 7T sequence and 3T \( \times 2 \times 2 \times 4 \) produced similar values of 0.041 ± 0.014 and 0.040 ± 0.008, respectively, while the 3T \( \times 3.5 \times 3.5 \times 4 \) protocol was more efficient at 0.086 ± 0.012. In terms of the SNR, both 3T sequences produced higher values than the 7T sequence; however, only the 3T \( \times 3.5 \times 3.5 \times 4 \) sequence was significant higher (\( p = .026 \)). These average SNR values were 2.8 ± 1.1 for 7T, 3.5 ± 0.5 for 3T \( \times 2 \times 2 \times 4 \) and 4.7 ± 0.8 for 3T \( \times 3.5 \times 3.5 \times 4 \). This is also reflected in the SNR efficiency: 0.158 ± 0.067 for the 7T protocol, 0.196 ± 0.028 for the 3T \( \times 2 \times 2 \times 4 \) protocol and 0.328 ± 0.053 for the 3T \( \times 3.5 \times 3.5 \times 4 \) protocol. Figure 7A shows exemplary images of raw label images with and without inversion pulses for background suppression. With those additional pulses, the raw data signals of all slices, except the first and the last ones (due to possible motion correction errors), are suppressed by 54%, on average, at 7T, 52%, on average, at 3T \( \times 2 \times 2 \times 4 \) and 54%, on average, at
So 7T showed an approximately equal amount of suppression. In Figure 7B, sample CBF images from both scanners with inversion pulses for background suppression are presented.

**DISCUSSION**

In this work, a hybrid $B^+\text{-phase-shim}$ algorithm for 7T pcASL perfusion brain imaging was introduced and evaluated. In
addition, the impacts of gradient adaptions and inversion pulses in terms of background suppression were examined. The hybrid $B^+$-shim and the adaption of the gradient strength lead to improved pcASL labeling and the additional inversion pulses lead to further progress, according to the pcASL image quality. Using these modifications, pcASL at 7T can be further improved, even under suboptimal $B^+$ conditions, SAR constraints and limited RF-coil coverage. These improvements were quantified relative to a conventional 3T pcASL sequence with background suppression pulses. For the resolution-matched protocol, 7T performed as well as 3T when using a standard head RF coil.

The $B^+$-phase-shimming used in this work performed well and improved the labeling. This improvement was directly evaluated in GRE images (significant gain = 23.6%) as well as through the tSNR and SNR of the perfusion signal: $+11\%$/$+11\%$ (non-significant). The mean flip angle of the proposed approach was $16.11 \pm 1.47^\circ$ (calculated from

**FIGURE 6** tSNR and SNR values for experiment 3. A, The tSNR of the 7T sequence, with and without inversion pulses for background suppression. The additional background suppression pulses lead to a 50% higher tSNR, on average. B, The SNR comparison for the 7T sequence with and without inversion pulses is shown. There is an average SNR gain of 75% with the inversion pulses. C,D, show the comparisons of 7T with the resolution-matched sequence at 3T and the lower-resolution sequence at 3T (all three sequences use inversion pulses for BS). According to the tSNR values, 7T performs as well as the resolution-matched 3T protocol. The SNR comparison shows higher values for 3T compared to 7T but no significant difference from the resolution-matched protocol.
the Bloch results), which is slightly higher than the mean obtained by Tong et al., who used a $B_1^+$ phase and amplitude shim. Nevertheless, above a certain level of tSNR/SNR, the phase-shim showed no improvement over the standard CP mode. However, the V3 segments of the corresponding subjects were located further up in the coil compared to the other subjects due to a relatively small head size, leading to higher $B_1^+$ per voltage. In future evaluations, the actual flip angles of the labeling pulses could be measured. However, doing so would require the implementation of a dedicated $B_1^+$ mapping sequence with integrated labeling pulses, a set-up that was beyond the scope of this work.

The Bloch simulations of the pcASL labeling showed high potential in terms of adapting the maximum gradient to improve the labeling efficiency at 7T. This potential applies in particular to suboptimal $B_1^+$ amplitudes, where higher $G_{\text{max}}$ values resulted in poorer performances compared to lower $G_{\text{max}}$ values. These results agree with the findings of Zhao et al., who improved the labeling robustness against off-resonances at 3T. Thus, in our work as well as in that of Zhao et al., a maximum gradient of around 3.5 mT/m, constrained by the labeling location and vessel anatomy, seems to be a robust option for pcASL at 7T. Therefore, lower gradients increase the labeling efficiency both for suboptimal $B_1^+$.
and $B_0$ inhomogeneity. However, the latter requires further examination at 7T.

Furthermore, the influence of inversion pulses on background suppression at 7T was examined in experiment 3. At 3T, additional BS pulses are widely used\(^\text{22,39}\); however, at 7T, SAR constraints limit the use of adiabatic pulses. It is important to note that even with 40% reduced amplitudes for non-selective adiabatic pulses, the pcASL images could be significantly improved (compare Figures 6 and 7). To facilitate reasonable 7T-to-3T comparisons, the 3T protocols were adjusted to match the resolution and acquisition time of the 7T protocol (3T\(_2 \times 2 \times 4\)) as well as the theoretically expected intrinsic SNR gain from 3T to 7T by lowering the 3T resolution (3T\(_{3.5} \times 3.5 \times 4\)). However, the comparison did not include the beneficial prolonged T\(_1\)-times at 7T. Furthermore, higher background suppression as well as more time-efficient sequence parameters could be used at 3T\(_{39}\) (see Supporting Information Figure S1, which is available online). Yet, doing so did not seem to have much impact on the field strength comparison (see Supporting Information Figure S1); therefore, the same parameters used at 7T were used at 3T for comparability. The results showed equal tSNRs at 7T and 3T in the resolution-matched protocol, but a lower tSNR at 7T than in the low-resolution protocol. In the work of Tong et al.,\(^\text{14}\) who also used parallel transmission without any hardware modifications, 7T only performed as well as 3T when the 3T pcASL labeling flip angle was truncated. However, in this work, inversion pulses for background suppression were used, whereas Tong et al. only used pre-saturation pulses. Furthermore, Tong et al. used higher maximum gradients (6 mT/m), which lead to decreased labeling efficiency at suboptimal $B_1^+$ conditions, as shown in this work. In terms of SNR, 7T performed worse than the low-resolution protocol at 3T, but there was no significant difference compared to the resolution-matched protocol at 3T. One possible reason for this finding may be that at 3T, only a 64-channel head coil was available for this work while at 7T a 32-channel head coil was used, which perhaps biased the SNR comparison. With dielectric pads, Zuo et al.\(^\text{20}\) showed a four-times improved SNR for 7T compared to 3T in a single-slice acquisition. Our CBF quantification at 7T showed no significant difference from that at 3T (see Supporting Information Table S2).

The labeling efficiency could be further improved by an incorporation of $B_0$-maps into the pulse design. The hybrid $B_1^+$-phase-shim design proposed in this work did not take $B_0$ inhomogeneity into account, as was done in Ref. [15]. In contrast, only vendor-provided $B_0$-shimming up to the partial third-order was placed over the imaging and labeling volume. An even better strategy to counteract $B_0$ inhomogeneity and improve $B_1^+$ would be to apply dynamic parallel transmission pulses. However, such pulses are challenging due to the requirements needed for the pcASL labeling to fulfill the conditions of the flow-driven adiabatic inversion.\(^\text{10}\) As alternative solutions, a pre-scan based method\(^\text{44}\) or a prospective correction\(^\text{45}\) could be applied to reduce artifacts that are caused by $B_0$ inhomogeneity.

Besides the incorporation of $B_0$ into the pulse design, the proposed approach does not incorporate SAR constraints into the optimization algorithm, as it was done in Ref. [15]. Which means, that this has to be balanced by extended TRs of the 7T measurements. Regardless, including SAR constraints in the optimization of this approach should be evaluated in future work.

A major limitation of this study was the limited coverage of the 7T coil. Consequently, the labeling plane had to be located within the V3 segment, which limited the labeling thickness. As a result, the optimum gradient amplitude indicated by the simulation could not be applied. At 3T, the suggestion is to label below the V3 segment when optimized gradient strategies are applied.\(^\text{38}\) However, for 7T, doing so would require a head/neck coil with transmitter channels located in the neck region, which was not available for this work.\(^\text{46}\) Furthermore, due to SAR limitations at 7T, it was necessary to use VERSE-modified labeling pulses to maintain a reasonable TR and corresponding measurement time. Although these pulses are known to be sensitive to $B_0$ off-resonances, Bloch simulations turned up no significant differences with regard to the labeling efficiency with and without VERSE (ratio = 1.02 ± 0.01, data not shown), which is in agreement with the investigations conducted by Boland et al.,\(^\text{14}\) who also found high labeling efficiencies over a wide range of off-resonances with VERSE pulses. Moreover, the SNR estimation used herein has a limitation in that the noise within the subtracted image does not necessarily have a Gaussian distribution. However, as this approach is commonly used,\(^\text{17,18,35,36}\) it was chosen to ensure comparability. Additionally, the 2D GRE-EPI readout used in this study makes whole-brain coverage difficult, especially as it pertains to the inferior cortex and cerebellum, mainly due to susceptibility artifacts.\(^\text{47}\) Finally, the $B_1^+$ inhomogeneity of the readout was not taken into account, leading to SNR loss.\(^\text{15}\) Therefore, the SNR could be enhanced by exploiting dynamic parallel transmission pulses\(^\text{40}\) for the readout; however, this enhancement was beyond the scope of this work.

Despite these limitations, $B_1^+$-phase-shimming, gradient adaptions and inversion pulses for background suppression are promising tools for improving pcASL labeling at 7T.

5 CONCLUSIONS

In conclusion, the combination of the proposed hybrid homogeneity and efficiency of $B_1^+$-phase-shim with individually adapted maximum gradients shows high potential for an improved pcASL labeling strategy under suboptimal $B_1^+$ conditions at 7T. Finally, 7T perfusion images can be further improved by using inversion pulses for background...
suppression. Under this regime, 7T performed as well as a resolution-matched 3T pcASL protocol without hardware changes.

DATA AVAILABILITY STATEMENT
The optimization code can be shared upon request, subject to the usual formalities.

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**SUPPORTING INFORMATION**

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

**FIGURE S1** Three volunteers were measured at 7T and 3T. At 3T, three different protocols were applied at both resolutions (2 × 2 × 4 mm² and 3.5 × 3.5 × 4 mm²): (1) a fast protocol without slice-selective inversion pulses for background suppression but three non-selective inversion pulses for BS (TIs: 1788 ms/214 ms/10 ms) and pre-saturation pulses with TS = 3300 ms, leading to TR = 4100 ms and therefore 80 label/control pairs in the same TA for the high-resolution protocol and a TA of 2:42 min for the low-resolution protocol; (2) a protocol with the parameters described in the main body of this paper (parameters at 7T), (3) a highly-background-suppressed protocol with pre-saturation pulses featuring two slice-selective and three non-selective inversion pulses (timings: TS = 5000 ms, TIslice-set = 4979 ms/4659 ms, Tinon-set = 1788 ms/214 ms/10 ms), leading to an average suppression of 36% for all evaluated slices. For both resolutions, no significant differences were found between the matching protocol and the faster or highly-background-suppressed protocol with regard to tSNR and SNR

**TABLE S1** Parameters of the B(1)+ mapping sequence and the TOF sequence used for the vessel identification in the hybrid B(1)+-shim routine at 7T

**TABLE S2** Gray matter CBF ratios of 7T to 3T for every volunteer and mean value. No significant variations are observable

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