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Simultaneous Measurement of Brain Perfusion and Labeling Efficiency in a Single Pseudo-Continuous Arterial Spin Labeling Scan

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Purpose: The aim of this study was to propose, optimize, and validate a pseudo-continuous arterial spin labeling (pCASL) sequence for simultaneous measurement of brain perfusion and labeling efficiency.

Methods: The proposed sequence incorporates the labeling efficiency measurement into the postlabeling delay period of a conventional perfusion pCASL sequence by using the time-encoding approach. In vivo validation experiments were performed on nine young subjects by comparing it to separate perfusion and labeling efficiency sequences. Sensitivity of the proposed combined sequence for measuring labeling efficiency changes was further addressed by varying the flip angles of the pCASL labeling radiofrequency pulses.

Results: The proposed combined sequence decreased the perfusion signal by ~4% and a lower labeling efficiency (by ~10%) was found as compared to the separate sequences. However, the temporal signal-noise-ratio of the perfusion signal remained unchanged. When the pCASL flip angle was decreased to a suboptimal setting, a strong correlation was found between the combined and the separate sequences for the relative change in pCASL perfusion signal as well as for the relative change in labeling efficiency. High correlation was also observed between relative changes in perfusion signal and the measured labeling efficiencies.

Conclusion: The proposed sequence allows simultaneous measurement of brain perfusion and labeling efficiency with high time-efficiency at the price of only a small compromise in measurement accuracy. The additional labeling efficiency measurement can be used to facilitate qualitative interpretation of pCASL perfusion images. **Magn Reson Med 79:1922–1930, 2018. © 2017 The Authors Magnetic Resonance in Medicine published by Wiley Periodicals, Inc. on behalf of International Society for Magnetic Resonance in Medicine. This is an open access article under the terms of the Creative Commons Attribution NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.**

Key words: pseudo-continuous; arterial spin labeling; perfusion; labeling efficiency; MRI

INTRODUCTION

Arterial spin labeling (ASL) is an MR technique for noninvasive and quantitative measurement of cerebral blood flow (CBF) by using the arterial blood as an endogenous tracer (1,2). Pseudo-continuous ASL (pCASL) is now the most widely accepted ASL approach mainly due to its high signal-noise-ratio (SNR) and easy implementation on clinical MR scanners without the need of additional hardware (3). In principle, the labeling (or inversion) of pCASL is achieved by applying a long series of short RF pulses in combination with a net mean gradient in the slice selection direction that manipulates the phase of the flowing spins resulting in a pseudo-adiabatic, flow-driven inversion. Consequently, its efficiency is vulnerable to factors like flow velocity and field inhomogeneities (4,5), and may vary among arteries, scans, and subjects. Careful optimization of the pCASL sequence can minimize such effects (6–8), albeit not prevent them completely. Because the measured CBF values scale linearly with the labeling efficiency, it is one of the most important parameters to estimate to allow accurate CBF quantification of pCASL perfusion scans (3).

Traditionally, as well as according to the consensus statement, a constant value (e.g., 0.85) as obtained from simulations is adopted for the labeling efficiency of pCASL in perfusion quantification (3). Recently, two methods were proposed to estimate the labeling efficiency of pCASL. In the first method, the labeling efficiency is indirectly estimated by comparing the mean CBF as obtained from a phase contrast (PC) scan at the carotid artery level to the mean CBF value of the whole brain pCASL scan (9). The drawback of this method is that it has difficulty in estimating artery-specific labeling efficiency, and that it relies on a careful selection of imaging parameters of the PC scan (10), as well as dedicated postprocessing of the PC, pCASL and the 3D T_1 anatomical images. Besides, a large cohort study showed that this method may be not suitable for calibration of labeling efficiency in individual subjects (11).

The alternative and direct method is an adaptation of a normal pCASL scan that monitors the arterial ASL signal

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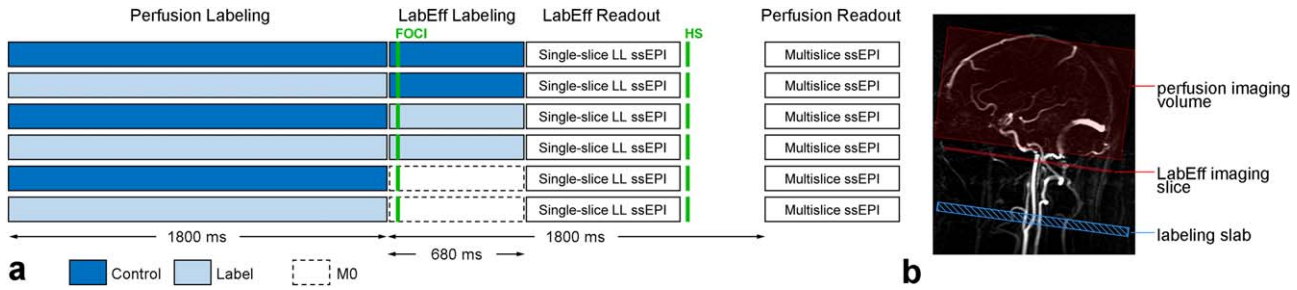

FIG. 1. Diagram (**a**) of the combined perfusion and labeling efficiency (LabEff) sequence and its planning (**b**). The LabEff module consists of a 680 ms labeling and a single-slice Look-Locker (LL) single-shot EPI (ssEPI) readout, and involves acquisition of three conditions: control, label and M0. The M0 acquisition is similar to the control condition, albeit with the RF switched off, to acquire the equilibrium arterial blood signal. In the combined sequence, the LabEff module is inserted into the postlabeling delay period of a conventional perfusion pCASL sequence, while the labeling conditions are arranged in a time-encoding manner. Two inversion pulses, i.e., one slab-selective FOCI pulse during and one unselective HS inversion pulse after the labeling, are included for background suppression. The labeling slab is placed slightly above the carotid bifurcation with the LabEff imaging slice inferior to the perfusion imaging volume and oriented perpendicular to the ICAs.

immediately after the labeling has stopped by means of a dynamic, high spatial resolution readout; from the observed passage of the labeled spins the artery-specific labeling efficiency can be estimated by taking into account the transport time between the labeling and the imaging planes (12). This method was shown to have great potential for addressing the variation of labeling efficiency resulting from factors like flow velocity and field inhomogeneities.

The common drawback of the above two labeling efficiency measurement methods is that one or two additional scans are needed and that these methods, therefore, come with a time-penalty. This could limit their clinical acceptance, especially considering the fact that the perfusion pCASL scan is already relatively long (~3–5 min). However, when looking carefully at the pCASL sequence, the main cause of the long scan duration is the long (~1800 ms) postlabeling delay (PLD) along with a similarly long labeling duration. Especially the PLD period can be considered to be time inefficient, because during this module only a couple of inversion pulses are executed to achieve optimal background suppression. The goal of this study was to study whether this PLD period could be exploited to include a labeling efficiency measurement, thereby obtaining a labeling efficiency measurement without an SNR- or time-penalty for the perfusion measurement. This study also explored the feasibility of using the combinedly measured labeling efficiency to enhance the qualitative interpretation of pCASL perfusion images by showing an example in which the labeling efficiency differed for the left and right internal carotid arteries.

Time-encoded ASL is a recently proposed approach for highly time-efficient multiple-PLD pCASL imaging (13,14). This technique divides the conventional labeling preparation module into multiple sub-blocks, and allows separation of the labeling bolus originating from different sub-blocks by means of a postprocessing procedure. In this study, the labeling efficiency module was incorporated into the PLD of a traditional perfusion pCASL sequence by using time-encoding principles.

METHODS

Combined Perfusion and Labeling Efficiency Sequence

The combined perfusion and labeling efficiency ("LabEff") sequence incorporates the LabEff module into the PLD of a conventional perfusion pCASL sequence (Fig. 1a). The LabEff-module consists of a short labeling block (chosen as 680 ms in this study) followed by a single-slice Look-Locker echo planar imaging (EPI) readout (12). Labeling efficiency is defined as the difference between control and label divided by twice of the equilibrium arterial blood signal. Because the control condition is not perfect, three types of LabEff-conditions need to be acquired: control, label and M0. The M0 acquisition is similar to the control condition, albeit with the RF switched off, to acquire the equilibrium arterial blood signal. Within the combined sequence, the perfusion-part remains identical to a standard pCASL perfusion scan, except that the first background suppression inversion pulse, which is executed during the LabEff labeling module, is made slice-selective (for this purpose a slice-selective frequency offset corrected inversion (FOCI) pulse is used instead of the conventional hyperbolic secant (HS) pulse as included in the standard scanner software). The FOCI pulse is applied on a 200-mm-thick slab superior to the labeling plane.

To reduce the interference between the two sub-parts, time-encoding principles are used for the labeling modules, i.e., the perfusion labeling condition is varied as control-label-control-label-control-label, while the LabEff labeling condition is varied as control-control-label-label-M0-M0. Similar to the previous implementation of background suppression for time-encoded ASL (14), the control (label) labeling condition is switched to label (control) after the first background suppression inversion pulse. Note that in the original, separate LabEff sequence a saturation pulse with a slab thickness of 80 mm, is applied superior to the imaging plane immediately before the start of the Look-Locker readout to suppress venous signal (12). However, this saturation pulse has to be discarded from the combined sequence, because it would interact with the perfusion measurement (see Discussion). The two sub-parts within the combined sequence share the same labeling slab that is placed slightly above the carotid bifurcation, whereas the LabEff imaging slice is positioned inferior to the perfusion imaging volume and planned through the beginning of the C2 segment of both internal carotid arteries (ICAs), as shown in Figure 1b. This imaging slice is orientated as perpendicular as possible to the two ICAs. The combined sequence was implemented using an interleaved scanning framework (15).

MRI Experiments

All MR experiments were approved by the local Institutional Review Board and were conducted on a 3T Philips Achieva scanner (Philips, Best, The Netherlands) with a 32-channel head coil. Nine healthy subjects (six males; mean age, 26.4 years) were included for the in vivo experiments after written informed consent was obtained. These in vivo MR experiments were performed to evaluate the performance of the combined perfusion and LabEff sequence by comparing it to the separate perfusion and LabEff sequences. The same parameters of the pCASL labeling used for all three sequences were as follows: balanced pCASL, radio frequency (RF) pulse duration = 0.5 ms, RF interval = 1.2 ms (i.e., 0.7 ms pause between RF pulses), RF flip angle (FA) = 22°, mean gradient strength = 0.6 mT/m, maximum gradient strength = 6 mT/m. All the pCASL sequences had the same labeling plane (Fig. 1b).

The other parameters for brain perfusion imaging were as follows: multi-slice single-shot EPI, field of view (FOV) = 240 × 240 × 114 mm^3, voxel size = 3 × 3 × 6 mm^3, number of slices = 19, repetition time/echo time (TR/TE) = 4206 ms / 9.6 ms, sensitivity encoding (SENSE) factor = 3, excitation RF FA = 90°, labeling duration = 1800 ms, PLD = 1800 ms, two background suppression pulses (i.e., a slice-selective FOCI pulse and a non–slice-selective HS pulse) at 1820 ms and 3155 ms after the start of the labeling, 30 repetitions of control/label pairs. The other imaging parameters of the LabEff scan were: shortest PLD as possible, single-slice Look-Locker EPI readout with 19 time-points at a 33.8 ms time-interval, FOV = 220 × 220 mm^2, voxel size = 2 × 2 × 3 mm^3, TR/TE = 1800 ms / 12 ms, excitation RF FA = 90°, SENSE factor = 2.5, partial Fourier factor = 0.71, 20 repetitions of control/label/M0 pairs.

To further address the sensitivity of the combined sequence for measuring the labeling efficiency, all above scans were repeated with a decreased FA of the pCASL RF pulses (three subjects with FA of 10°, three with 15°, and three with 18°). At these smaller pCASL FAs, a lower labeling efficiency is expected, thereby enabling to study whether the combined sequence is equally suited as the separate sequence to detect this lower efficiency.

Moreover, an M0-scan as well as a vessel-encoded arterial spin labeling (VEASL) (16) scan were performed to allow normal quantification of the CBF as well as to identify the arterial flow territories. Finally, a high-resolution (1.2 × 1.2 × 1.2 mm^3) 3D T_1-weighted (T_1W) MP-RAGE scan was performed to obtain masks of brain and gray matter (GM).

Processing of Brain Perfusion Data

The raw pCASL images were motion corrected and the M0- and 3D-T_1-scans were co-registered to these scans. From the registered 3D T_1W images, the brain and GM masks were extracted. All these processings were performed with SPM12 (http://www.fil.ion.ucl.ac.uk/spm). Subsequently, quantification of the CBF map was performed by using the motion corrected perfusion images and the M0-scan, while assuming a constant labeling efficiency of 0.85 (3). Additionally, the temporal SNR (tSNR) map was calculated from the ASL-subtraction images as the mean signal divided by the standard deviation across repetition. The motion corrected VEASL images were used to obtain the perfusion territories of basilar artery (BA), right and left internal carotid arteries (RICA and LICA) by using a k-means clustering algorithm (17). Note that, because of the time-encoding scheme as shown in Figure 1, the brain perfusion images of the combined sequence can be processed in an identical way as a separate perfusion scan. Based on the obtained CBF, tSNR and masks, whole-brain GM CBF, whole brain GM tSNR, territorial GM CBF and territorial GM tSNR were calculated.

Processing of Labeling Efficiency Data

The data of the separate LabEff scan were processed in a similar way as in the original publication (12). In brief, within the artery of interest, voxels with the highest LabEff difference signal (i.e., the amplitude of the complex difference of control and label time curves) were identified, and their LabEff difference signals were for each time-point individually normalized by the corresponding M0-signals at that time-point (such way of normalization was aimed to alleviate the residual influence of the preceding venous signal suppression pulse). The normalized LabEff difference signals will show a plateau phase followed by a downslope. These normalized signals were then averaged over the voxels-of-interest and the resultant downslope segment was used to calculate the labeling efficiency according to a hemodynamic model that compensates for the T_1 relaxation of the labeled spins occurring while flowing from the labeling to the imaging plane. Note that contrary to the previous study (12), this study used a separately measured M0-signal instead of the control signal for the normalization.

For the combined sequence, the LabEff time signals were processed in a similar way, although the LabEff difference signal was now normalized by a single M0-value that was obtained from the last time-point before the second background suppression inversion pulse, which was least perturbed by the background suppression inversion pulses (see Discussion). For each LabEff scan, labeling efficiency values of the RICA and LICA were calculated.

Statistical Analysis

Paired t-tests were performed to test for differences between the combined and the separate measurements. These tests were performed for the whole brain GM CBF, whole brain GM tSNR, territorial GM CBF, territorial GM tSNR, and labeling efficiency. Furthermore, the relative changes of the whole brain GM CBF, territorial GM CBF and arterial labeling efficiency between the values obtained with the lower pCASL FA (i.e., 10°, 15°, or 18°) and the values obtained with FA of 22° were calculated. For example, for the whole brain GM CBF acquired with pCASL FA of 15° and 22°, the relative change was calculated as 100% × (CBF_15° - CBF_22°) / CBF_22°. Subsequently, the relative changes were compared using paired t-tests. In addition, Pearson correlation coefficients were calculated between the combined and the separate sequence, and between the perfusion and labeling efficiency measurements. For all statistical tests, a *P*-value of 0.05 was considered as statistically significant.

Table 1
Comparison of GM CBF and tSNR Between the Separate and the Combined Sequences.

	CBF [ml/100g/min]			tSNR [a.u.]		
	Separate	Combined	*P*-Value	Separate	Combined	*P*-Value
Whole brain	45.1 ± 7.8	43.3 ± 8.0	0.028*	2.0 ± 0.3	2.0 ± 0.4	0.953
RICA	45.8 ± 6.5	44.2 ± 6.4	0.049*	1.9 ± 0.2	1.9 ± 0.3	0.782
LICA	46.8 ± 8.1	45.8 ± 8.7	0.138	1.9 ± 0.3	1.9 ± 0.4	0.820
BA	45.8 ± 9.5	42.9 ± 9.7	0.013*	2.4 ± 0.4	2.4 ± 0.5	0.947

*Indicates statistically significant with *P*-value < 0.05; only data acquired with pCASL FA of 22° are included.

RESULTS

Perfusion Measurement

Mean CBF and tSNR for both whole brain GM and territorial GM as measured by the separate and the combined sequences with a pCASL FA of 22° are shown in Table 1. The GM CBF values as measured by the combined sequence were ~4% smaller than when measured with the separate sequence, although not all paired comparisons showed a statistically significant difference. The GM tSNR of the separate and the combined sequence were similar. Figure 2 shows representative CBF maps as acquired by the two sequences.

Labeling Efficiency Measurement

Typical curves observed within the ICA as acquired with both the combined as well as the separate sequences are shown in Figure 3. According to the curves of the separate LabEff sequence, the control time signal was slightly lower than the M0 time signal, especially during the first time-points, demonstrating that the control time signal cannot be assumed equal to the M0 time signal. This suggests that it is necessary to acquire the M0 time signal separately for accurate labeling efficiency calculation. The obtained ICA labeling efficiencies of the two sequences are shown in Table 2. The labeling efficiency by the combined sequence was found to be ~10% lower as compared to the separate sequence, although the statistical tests did just not reach significance.

Relative Changes of the Measurements with Different pCASL FAs

The GM CBF of the ICA flow territories obtained with the separate pCASL perfusion scan decreased by 54% (range, 46%–68%), 29% (range, 24%–35%), and 12% (range, 1%–25%) when the pCASL FA was lowered from 22° to 10°, 15°, and 18°, respectively. There was no significant difference between the relative changes in labeling efficiency as measured with the separate and the combined sequences, whereas the relative change in GM CBF was smaller for the combined than for the separate sequence (Table 3). In addition, there was no significant difference between the relative change in labeling efficiency and the relative change in GM CBF (all $P > 0.05$). More importantly, the relative changes in GM CBF and labeling efficiency were strongly correlated (Fig. 4).

Figure 5 shows the results of an additional proof-of-concept experiment on one healthy subject (male, 27 years) to illustrate the potential of the measured labeling efficiency to be used to facilitate the qualitative interpretation of pCASL perfusion images.

DISCUSSION

In this study, a highly time-efficient pCASL sequence was proposed, implemented and validated that allows simultaneous measurement of brain perfusion and artery-specific labeling efficiency. Whereas both the CBF and labeling efficiency were underestimated as compared to the corresponding separate scans, the correlation analysis showed that the proposed combined sequence has similar sensitivity for detecting perfusion and labeling efficiency changes. Moreover, the relative changes of perfusion and labeling efficiency were found to be highly correlated and quantitatively comparable, which indicates the feasibility as well as the need for using labeling efficiency measurement to facilitate the qualitative interpretation of pCASL perfusion images or to achieve correct quantification of pCASL perfusion values.

Both the perfusion and labeling efficiency were underestimated to some extent when measured by the combined sequence as compared to separate acquisitions. Because both sub-parts in the combined sequence are almost identical to their separate counterparts, these measurement discrepancies between the combined and the separate

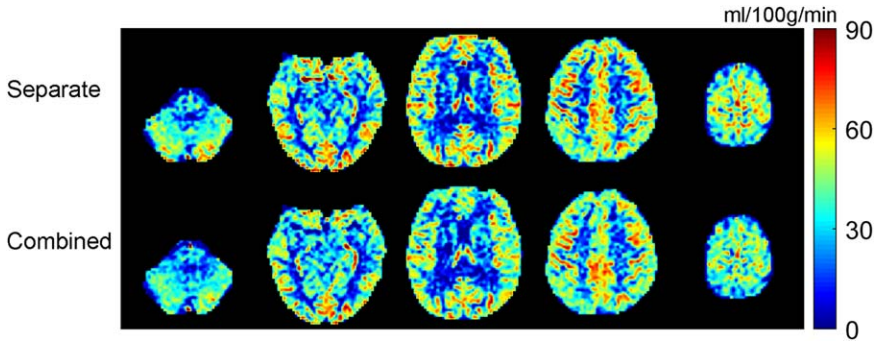

FIG. 2. Representative CBF maps of a subject as obtained by the separate (upper) and the combined (lower) sequences with a pCASL FA of 22°.

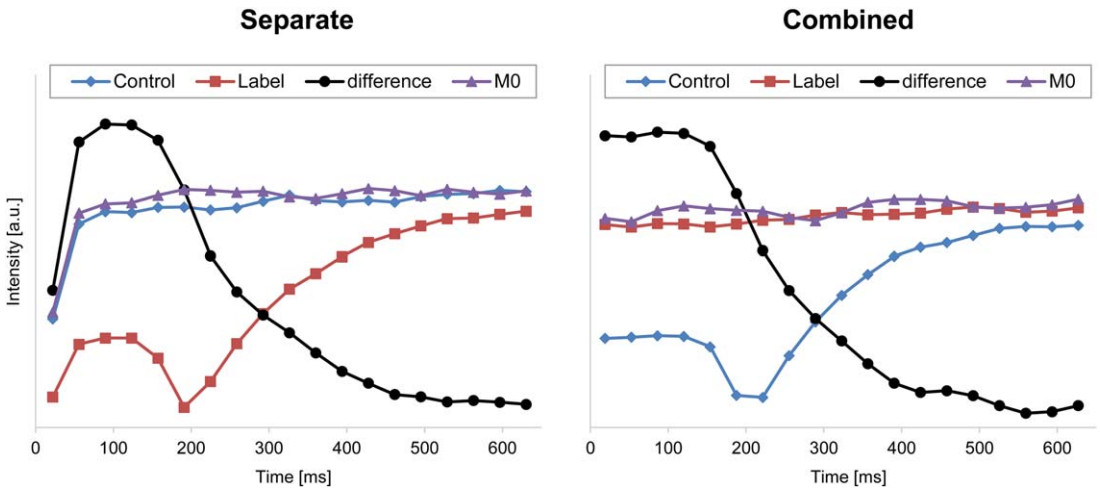

FIG. 3. Typical arterial signals acquired by the separate and the combined labeling efficiency measurement. The signals were taken from one voxel within the internal carotid artery that exhibited the largest difference signal intensity; the averaged curves over all repetitions are shown. The difference signal (black curve) represents the magnitude of the complex difference between the control and label signal. For the combined sequence, control and label signals were swapped after the first background suppression inversion pulse, because also during acquisition these conditions were swapped. Note that at the first time-point of the separate LabEff scan, the arterial blood signal was strongly attenuated by the saturation pulse that was performed immediately before the Look-Locker readout for venous signal suppression.

approaches should be largely explained by an interference between the two sub-parts. In the next two sections, this will be discussed for both the perfusion as well as the labeling efficiency measurement.

Perfusion Measurement

The slight underestimation of perfusion in the combined sequence (Table 1) may be explained by three factors. First, according to the LabEff time signals, we found that for some spins it takes more than 600 ms to flow from the labeling plane to the LabEff imaging plane, as can, e.g., be seen in Figure 3. Because there is only a 680 ms interval between the stop of the perfusion labeling and the start of the LabEff readout, some labeled spins with low flow velocity are likely to be saturated by the consecutive 90° excitation pulses of LabEff readout before entering the brain. This would cause fewer effective labeled spins for perfusion measurement to flow into the brain and thus a smaller perfusion signal for the combined sequence. The fact that the CBF underestimation for BA (or VAs) flow territory (~3 mL/100 g/min) was nearly twice that of ICAs (Table 1) seems to support this explanation, because the VAs were found to have smaller flow velocity and longer transit times between the labeling plane and the LabEff imaging plan than the ICAs (data not shown).

The second factor that could have led to an underestimation of the perfusion signal may be the induction of eddy currents by the LabEff readout. In preliminary experiments with a combined sequence that exhibited a long LabEff readout (~1000 ms) and thus a small pause between the end of the LabEff readout and the beginning of the perfusion readout, an artifact in the brain pCASL images was observed that we attributed to eddy currents (Fig. 6). Therefore, a much shorter total readout time of the LabEff module (642 ms) has been adopted in the current experiments, which has limited the severity of this artifact, although some residual effects might still be present.

Third, an imperfect cancellation of the LabEff labeling in the decoding process caused by, e.g., cardiac pulsations may also result in perfusion signal loss. Nevertheless, it is important to note that despite the observed perfusion underestimation, tSNR of the perfusion measurement by the combined sequence was not significantly lower as compared to the separate sequence.

Labeling Efficiency Measurement

As mentioned before, the labeling efficiency as measured in the ICAs by the combined sequence was smaller than

Table 2
Comparison of Labeling Efficiency Measured by the Separate and the Combined Sequences.

	Separate*	Combined*	*P*-Value
RICA	0.79 ± 0.09	0.70 ± 0.08	0.078
LICA	0.81 ± 0.08	0.74 ± 0.06	0.059

*Only data acquired with pCASL FA of 22° are included.

Table 3
Comparison Between the Separate and the Combined Sequences of the Relative Change in GM CBF and Labeling Efficiency When the pCASL FA Was Changed From 22° to a Sub-optimal Value (10°, 15°, or 18°).

	Separate [%]	Combined [%]	*P*-Value
CBF			
Whole brain	−30 ± 19	−26 ± 19	0.003*
RICA	−33 ± 19	−28 ± 20	0.020*
LICA	−30 ± 20	−27 ± 20	0.010*
BA	−27 ± 20	−23 ± 19	0.013*
Labeling efficiency			
RICA	−31 ± 21	−29 ± 20	0.530
LICA	−29 ± 21	−30 ± 18	0.727

*Indicates statistically significant with P-value < 0.05.

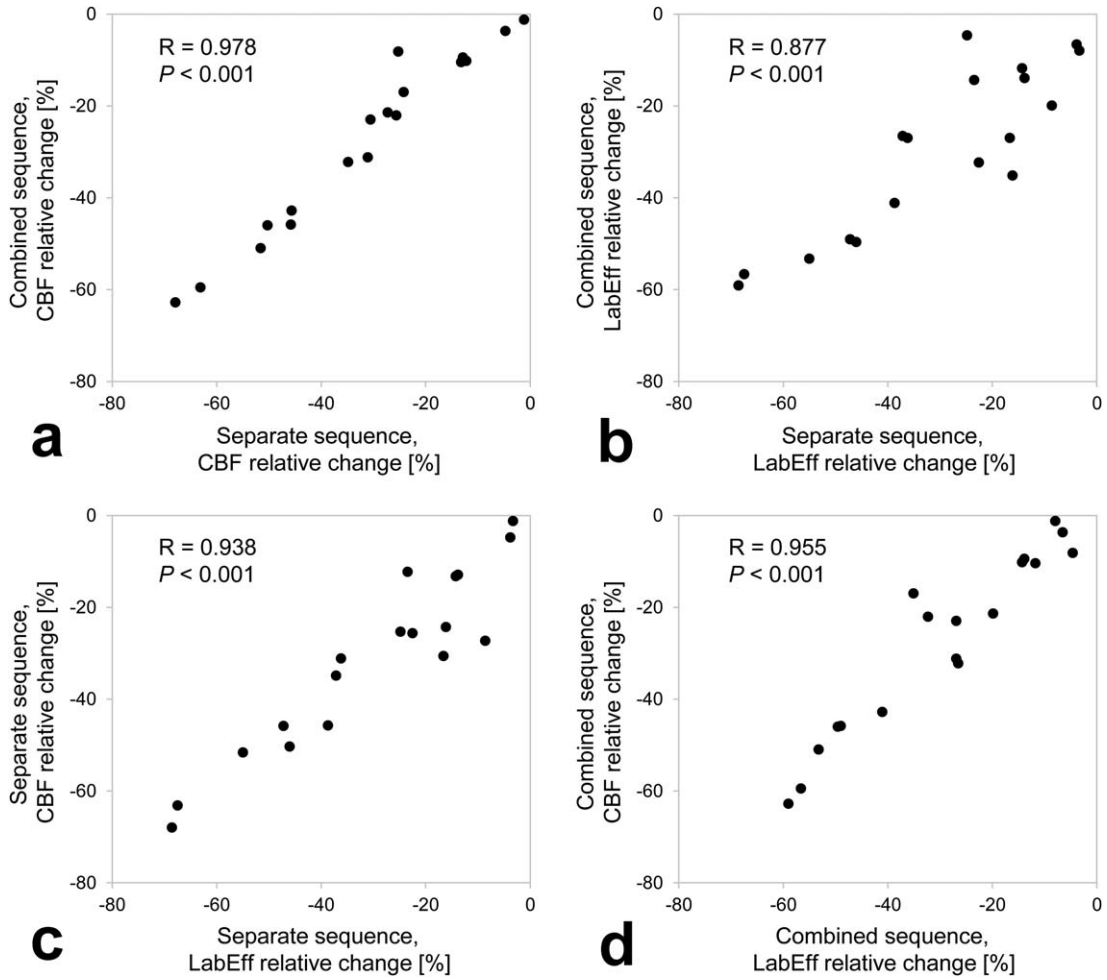

FIG. 4. **a**: Correlation of the relative change in observed GM CBF between the separate and the combined sequences. **b**: Correlation of the relative change in observed labeling efficiency (LabEff) between the separate and the combined sequences. **c,d**: Correlation between relative changes in GM CBF and LabEff as acquired with the separate (c) and the combined (d) sequences. The relative changes are defined as the relative change in GM CBF (or LabEff) when the pCASL flip angle was lowered from 22° to, respectively, 10°, 15°, or 18°.

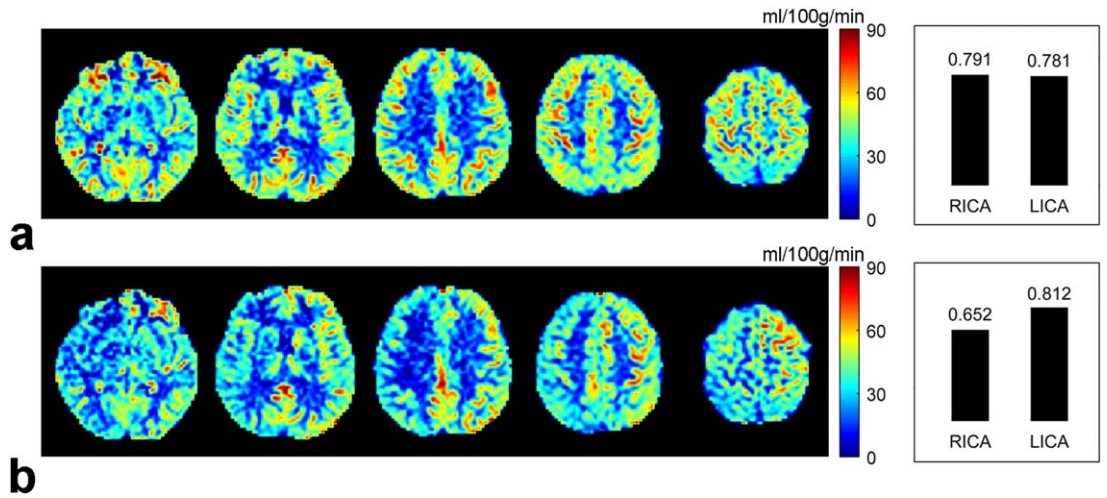

FIG. 5. Example images showing how the measured labeling efficiency (right) can be used to facilitate the qualitative interpretation of the pCASL perfusion images (left). **a**: CBF maps and labeling efficiency simultaneously measured by the proposed combined sequence, showing approximately equal labeling efficiency for right and left ICA. **b**: CBF maps and labeling efficiency simultaneously measured by the proposed combined sequence, with an extra in-plane gradient applied to the pCASL labeling pulse to create a labeling efficiency difference between right and left sides similar as to what may happen due to factors like B0 inhomogeneity or velocity differences. In this example, the measured labeling efficiency can be used to confirm that the low perfusion signal on the right anterior circulation is mainly caused by the suboptimal labeling efficiency in the RICA.

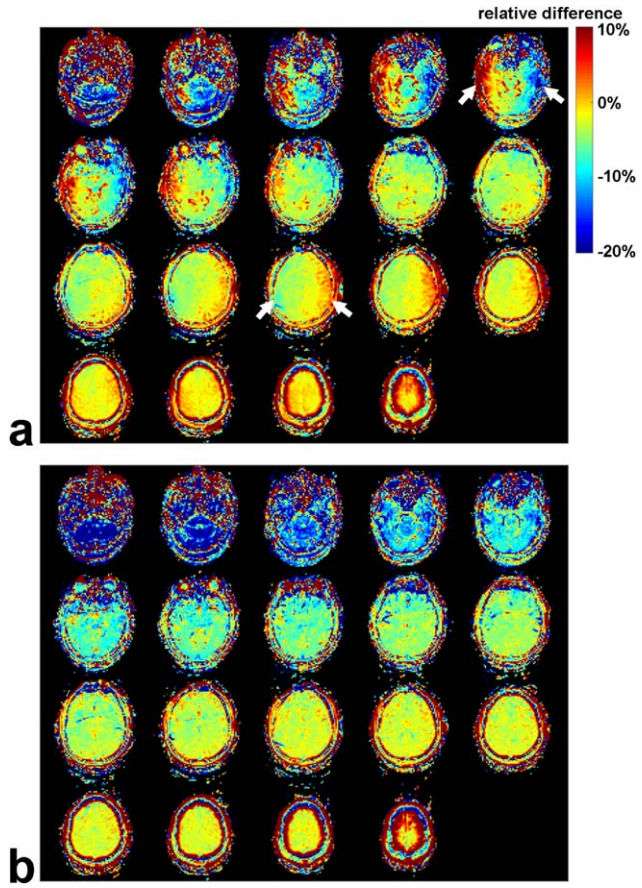

FIG. 6. Relative difference between raw brain images of different perfusion pCASL scans, showing the artifacts caused by the LabEff readout in the combined sequence. **a**: Relative difference between the control images of the separate perfusion pCASL and the control images of a combined sequence exhibiting a long LabEff readout (1048 ms) and thus only a very short pause between the end of the LabEff readout and the start of the perfusion readout (~70 ms). **b**: Relative difference between the control images of the separate perfusion pCASL and a combined sequence with the shorter LabEff readout (642 ms) as used in all other experiments. As shown in (a), the combined sequence with long LabEff readout yielded images with artifacts (white arrow), which was attributed to eddy currents induced by the LabEff readout. These artifacts can no longer be identified when the readout time was lowered (b).

that measured by the separate LabEff sequence (see Table 2; although statistical testing did not reach significance, the observed trend cannot be ignored). Similarly, as argued above, the rear end of the bolus of the labeled spins for perfusion measurement may still have been present during the LabEff measurement, especially during the first time-points. This would reduce the effective blood compartment of LabEff difference signal, leading to an underestimation of the labeling efficiency. Moreover, especially in such large arteries it is unlikely that decoding of the time-encoded signal will be perfect, e.g., due to cardiac pulsation effects (12).

On the other hand, the accuracy of labeling efficiency calculation is dependent on both the measurement of the equilibrium blood signal (i.e., M0) and the difference signal. Unfortunately, the first background suppression inversion pulse, which is needed for the perfusion measurement, causes a large perturbation of the arterial blood signal. Specifically, when using the M0 normalization for each time-point, the perturbation would make the M0 time signal deviate from the true equilibrium signal especially for the earlier time-points. This effect was especially distinct for arteries with small flow velocity, like the VAs (Fig. 7). To circumvent these issues, a single time-point M0-signal was adopted for normalization in this study, which was taken from the time-point immediately before the second background suppression inversion pulse. As such the influence of the background suppression inversion pulse on the labeling efficiency measurement was minimized, particularly for the ICAs in which refreshment of spins is much faster due to the larger velocities.

To obtain a reliable labeling efficiency measurement, the proposed combined sequence should acquire a LabEff difference signal with a complete downslope and a LabEff M0-signal that at least at one time-point is almost unaffected by the preceding perfusion labeling and background suppression inversion pulses. These two requirements are largely dependent on the flow velocity and the total length the labeled spins have to travel between the labeling and the imaging planes. Although this results in a relatively complicated relation between the measurement reliability and flow velocity, fulfillment of the above two requirements can be directly identified from the acquired LabEff time signals. This can be done by, respectively, looking at whether there is a plateau phase in the LabEff difference signal before the downslope starts, and whether the M0 time signal reaches its steady state at the later time-points.

Relative Change

Although the combined sequence showed minor reductions in the measured pCASL perfusion signal and labeling efficiency as compared to the separate sequences, it did not impact the temporal SNR and it also was similarly effective in detecting changes in GM CBF and labeling efficiency, as demonstrated by the similar relative change values (Table 3) and the strong correlation of the change (Figs. 4a,b) between the combined and the separate sequences. Moreover, the relative change in the detected pCASL perfusion signal was very similar to the simultaneously measured change in labeling efficiency and the measures were highly correlated (Fig. 4d). This suggests that the labeling efficiency measurement has potential to be used to correct for quantification errors of perfusion measurement caused by imperfect labeling efficiency.

Nevertheless, due to the absence of a true gold standard, we are at the moment not able to directly verify the accuracy of the measured labeling efficiencies. In our opinion, this does not compromise the feasibility of using the measured labeling efficiency to facilitate qualitative interpretation of perfusion maps (Fig. 5).

Implementation Details of the Proposed Method

The proposed method of this study was made possible by combining two recent MRI innovations: the use of time-encoding of the labeled spins and the use of two

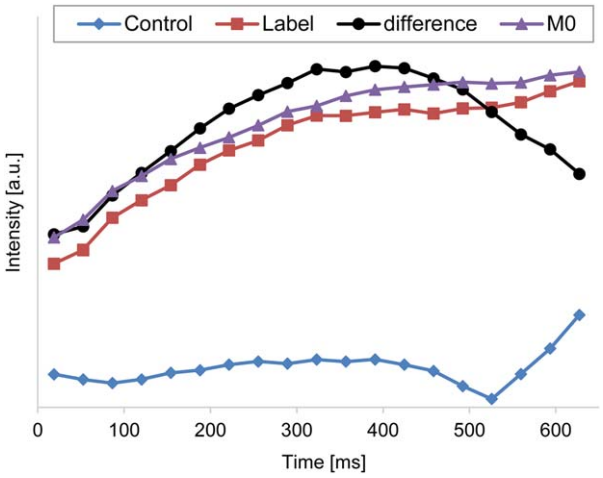

FIG. 7. Representative vertebral artery signals acquired by the combined labeling efficiency measurement, showing influence of the first background suppression inversion pulse. Because of the first background suppression inversion pulse (played out 660 ms before the start of the LabEff readout, i.e., at -660 ms on the displayed x-axis), the M0 time signal deviated severely from the true equilibrium during the first time-points while gradually recovering to the equilibrium value for later time-points. Similar influence of the background suppression inversion pulse is present in the control and label signals, but those are subtracted out in the LabEff difference signal.

different readout modules within a single sequence. The time-encoding approach in ASL has been shown to be a highly time-efficient and flexible strategy for obtaining dynamic ASL information, such as arterial transit time together with CBF perfusion, in a single pCASL scan (14,18,19). In contrast to these previous implementations, we did not use a true Hadamard encoding in this study (Fig. 1), because of the need for three different labeling conditions to enable the labeling efficiency measurement. Importantly, the used encoding still ensured the same SNR for the perfusion measurement as a similar non–time-encoded pCASL sequence of the same total scan time. A previous ISMRM abstract showed the feasibility of performing two different readouts within a single pCASL scan to enable simultaneous acquisition of angiography and perfusion images (18). In the current study, the two readouts were spatially nonoverlapping, thereby alleviating crosstalk between the two readouts. Furthermore, it is important to note that the SNR of the labeling efficiency measurement is more than sufficient when performed in the proposed combined sequence, which allows one to select the number of averages based upon the needed SNR for perfusion imaging; inclusion of a labeling efficiency measurement into a perfusion pCASL does not, therefore, lead to a need for increasing total scan time.

In our original publication on the separate LabEff sequence, a large saturation slab was performed immediately before the Look-Locker readout to suppress venous signal that otherwise would affect the measurement of the labeling efficiency in the ICAs (12). However, in the combined sequence, this saturation slab needs to be discarded because it would saturate the brain ASL signal as well. Fortunately, in the combined sequence, venous blood spins within the brain will undergo both the presaturation pulse and the background suppression inversion pulses of the perfusion imaging sub-part, resulting in relatively low venous signal when performing the LabEff measurement (data not shown). Therefore, the saturation pulse for venous signal suppression is deemed unnecessary for the combined sequence.

A limitation of the current combined sequence is that it is less suitable to measure the labeling efficiency of the VAs. Because the flow velocity in VA is generally smaller than in ICA, a longer Look-Locker readout (~1000 ms) would be needed to acquire the complete downslope of the LabEff difference signal. However, as mentioned above, a longer LabEff readout is more likely to cause eddy current-like artifacts in the brain pCASL images. Worse still, the LabEff M0 time signal of VA is severely affected by the background suppression inversion pulses, and even the single time-point M0-signal immediately before the second background suppression inversion pulse still suffers from these. Finally, in most subjects the VA suffers from more partial volume effects when using the current LabEff planning. Therefore, it would be difficult to obtain an accurate labeling efficiency measurement for VA with the current combined sequence, and we chose to optimize the sequence for ICA only.

Note that, in patients with low flow velocity in both RICA and LICA, the accuracy of labeling efficiency measurement can be maintained by shortening the distance between the labeling and the imaging planes for the LabEff sequence, to achieve accurate monitoring of the downslope of the LabEff difference signal. But when flow velocities would be too different, e.g., in patients with unilateral carotid artery steno-occlusive disease, the accuracy of labeling efficiency may be difficult to maintain for both ICAs. Because the ICAs are relatively straight at the proposed measurement location, the presented implementation can be considered rather insensitive to low flow velocities.

CONCLUSIONS

In conclusion, the proposed combined sequence allows simultaneous measurement of brain perfusion and artery-specific labeling efficiency in a single pCASL scan with an acquisition time equal to a conventional perfusion pCASL sequence. The combined sequence has similar sensitivity for detecting the ASL signal change as the separate perfusion pCASL and LabEff sequence, although it may to some extent underestimate the perfusion and labeling efficiency. The additional labeling efficiency measurement obtained by the combined sequence can be used to facilitate qualitative interpretation of pCASL perfusion images.

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REFERENCES

1. Telischak NA, Detre JA, Zaharchuk G. Arterial spin labeling MRI: clinical applications in the brain. J Magn Reson Imaging 2015;41: 1165–1180.
2. Detre JA, Rao H, Wang DJ, Chen YF, Wang Z. Applications of arterial spin labeled MRI in the brain. J Magn Reson Imaging 2012;35:1026–1037.
3. Alsop DC, Detre JA, Golay X, et al. Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: a consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia. Magn Reson Med 2015;73:102–116.
4. Wu WC, Fernandez-Seara M, Detre JA, Wehrli FW, Wang J. A theoretical and experimental investigation of the tagging efficiency of pseudocontinuous arterial spin labeling. Magn Reson Med 2007;58:1020–1027.
5. Dai W, Garcia D, de Bazelaire C, Alsop DC. Continuous flow-driven inversion for arterial spin labeling using pulsed radio frequency and gradient fields. Magn Reson Med 2008;60:1488–1497.
6. Zhao L, Vidorreta M, Soman S, Detre JA, Alsop DC. Improving the robustness of pseudo-continuous arterial spin labeling to off-resonance and pulsatile flow velocity. Magn Reson Med 2017;78: 1342–1351.
7. Jahanian H, Noll DC, Hernandez-Garcia L. B0 field inhomogeneity considerations in pseudo-continuous arterial spin labeling (pCASL): effects on tagging efficiency and correction strategy. NMR Biomed 2011;24:1202–1209.
8. Jung Y, Wong EC, Liu TT. Multiphase pseudocontinuous arterial spin labeling (MP-PCASL) for robust quantification of cerebral blood flow. Magn Reson Med 2010;64:799–810.
9. Aslan S, Xu F, Wang PL, Uh J, Yezhuvath US, van Osch M, Lu H. Estimation of labeling efficiency in pseudocontinuous arterial spin labeling. Magn Reson Med 2010;63:765–771.
10. Peng S-L, Su P, Wang F-N, Cao Y, Zhang R, Lu H, Liu P. Optimization of phase-contrast MRI for the quantification of whole-brain cerebral blood flow. J Magn Reson Imaging 2015;42:1126–1133.
11. Dolui S, Wang Z, Wang DJ, et al. Comparison of non-invasive MRI measurements of cerebral blood flow in a large multisite cohort. J Cereb Blood Flow Metab 2016;36:1244–1256.
12. Chen Z, Zhang X, Yuan C, Zhao X, van Osch MJ. Measuring the labeling efficiency of pseudocontinuous arterial spin labeling. Magn Reson Med 2017;77:1841–1852.
13. Guenther M. Highly efficient accelerated acquisition of perfusion inflow series by cycled arterial spin labeling. In Proceedings of the 15th Annual Meeting of ISMRM, Berlin, Germany, 2007. p. 380.
14. Teeuwisse WM, Schmid S, Ghariq E, Veer IM, van Osch MJ. Time-encoded pseudocontinuous arterial spin labeling: basic properties and timing strategies for human applications. Magn Reson Med 2014; 72:1712–1722.
15. Henningsson M, Mens G, Koken P, Smink J, Botnar RM. A new framework for interleaved scanning in cardiovascular MR: application to image-based respiratory motion correction in coronary MR angiography. Magn Reson Med 2015;73:692–696.
16. Wong EC. Vessel-encoded arterial spin-labeling using pseudocontinuous tagging. Magn Reson Med 2007;58:1086–1091.
17. Gevers S, Bokkers RP, Hendrikse J, Majoie CB, Kies DA, Teeuwisse WM, Nederveen AJ, van Osch MJ. Robustness and reproducibility of flow territories defined by planning-free vessel-encoded pseudocontinuous arterial spin-labeling. AJNR Am J Neuroradiol 2012;33: E21–E25.
18. Suzuki Y, Teeuwisse WM, Schmid S, Koken P, Van Cauteren M, Helle M, Van Osch M. Simultaneous acquisition of perfusion maps and 4D MR angiography by means of arterial spin labeling MRI. In Proceedings of the the 22nd Annual Meeting of ISMRM, Milan, Italy, 2014. p. 0720.
19. Schmid S, Teeuwisse WM, Lu H, van Osch MJ. Time-efficient determination of spin compartments by time-encoded pCASL T2-relaxation-under-spin-tagging and its application in hemodynamic characterization of the cerebral border zones. Neuroimage 2015;123: 72–79.