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MR fingerprinting ASL: Sequence characterization and comparison with dynamic susceptibility contrast (DSC) MRI

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Abstract

MR Fingerprinting (MRF)-based Arterial-Spin-Labeling (ASL) has the potential to measure multiple parameters such as cerebral blood flow (CBF), bolus arrival time (BAT), and tissue T_1 in a single scan. However, the previous reports have only demonstrated a proof-of-principle of the technique but have not examined the performance of the sequence in the context of key imaging parameters. Furthermore, there has not been a study to directly compare the technique to clinically used perfusion method of dynamic-susceptibility-contrast (DSC) MRI. The present report consists of two studies. In the first study ($N = 8$), we examined the dependence of MRF-ASL sequence on TR time pattern. Ten different TR patterns with a range of temporal characteristics were examined by both simulations and experiments. The results revealed that there was a significance dependence of the sequence performance on TR pattern ($p < 0.001$), although there was not a single pattern that provided dramatically improvements. Among the TR patterns tested, a

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SUPPORTING INFORMATION

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sinusoidal pattern with a period of 125 TRs provided an overall best estimation in terms of spatial consistency. These experimental observations were consistent with those of numerical simulations. In the second study ($N=8$), we compared MRF-ASL results with those of DSC MRI. It was found that MRF-ASL and DSC MRI provided highly comparable maps of cerebral blood flow (CBF) and bolus-arrival-time (BAT), with spatial correlation coefficients of 0.79 and 0.91, respectively. However, in terms of quantitative values, BAT obtained with MRF-ASL was considerably lower than that from DSC ($p < 0.001$), presumably because of the differences in tracer characteristics in terms of diffusible versus intravascular tracers. Test–retest assessment of MRF-ASL MRI revealed that the spatial correlations of parametric maps were 0.997, 0.962, 0.746 and 0.863 for B_1^+ , T_1 , CBF, and BAT, respectively. MRF-ASL is a promising technique for assessing multiple perfusion parameters simultaneously without contrast agent.

Keywords

arterial spin labeling; cerebral blood flow; dynamic susceptibility contrast perfusion imaging; gadolinium based contrast agent; magnetic resonance fingerprinting

1 | INTRODUCTION

Cerebral perfusion imaging plays a pivotal role in many brain diseases, including neurodegenerative diseases (e.g. Alzheimer's,^{1,2} Parkinson's,³ Huntington's⁴ diseases), psychiatric disorders (e.g. schizophrenia,⁵ depression,⁶ autism,⁷ ADHD⁸), and tumor (primary and metastatic brain tumor⁹). Dynamic susceptibility contrast (DSC) is the primary technique for perfusion MRI performed clinically and can estimate several hemodynamic parameters such as cerebral blood flow (CBF), cerebral blood volume (CBV), and time-to-peak (TTP).¹⁰ However, this technique requires the use of gadolinium (Gd) based contrast agent.

Arterial Spin Labeling (ASL) MRI allows for non-contrast-agent evaluation of CBF,^{11–14} and has the advantage of providing non-invasive and repeated measures. However, ASL MRI cannot yet replace DSC in routine clinical applications. An important reason is that most forms of ASL do not provide a measurement of timing parameters, such as TTP. Some forms of ASL, such as multi-delay ASL (using either separate acquisitions^{15–20} or with combined Look-Locker scheme^{21–23}), have been shown to provide an assessment of an equivalent parameter, bolus-arrival-time (BAT), with a temporal resolution potentially even greater than that in DSC. Nonetheless, its accuracy is restricted by the number of delay times used (typically 5 to 15) and has not been used widely in clinical applications. It is important to point out that, at least in cerebrovascular diseases, timing parameters have been shown to be highly sensitive in detecting deficit regions,^{24,25} thus is a desirable parameter in clinical trials.^{26–28}

MR Fingerprinting (MRF) based ASL has been recently proposed as a new approach to measure multiple hemodynamic parameters in a single scan.^{29–35} This novel sequence applies a time-varying acquisition scheme to allow separate encoding of different hemodynamic parameters in the MR image series, and the model-fitting was based on signal matching to database entries rather than based on analytical formulism.³⁶ Sensitivity of this

technique in detecting hemodynamic alterations has been tested using hypercapnia challenge, and clinical utility has been examined preliminarily in patients with stroke and moyamoya disease.^{29,35}

Due to the time-varying nature of MRF-type sequences, the sensitivity of the MRF signals to hemodynamic parameters, and thereby performance of MRF-ASL, is expected to be dependent on the pulse sequence parameters. In particular, the pattern of TR time series is one of the most important parameters in MRF-ASL and has not been systematically investigated. In this study we examined MRF-ASL results across ten different TR patterns that have a range of temporal characteristics. The experimental results were also compared to numerical simulations. Furthermore, we compared MRF-ASL hemodynamic maps to those obtained with Gd-based DSC MRI.

2 | METHODS

This study was approved by Johns Hopkins University Institutional Review Board. All subjects gave informed written consent before participation. All experiments were performed on a 3 T (Philips Healthcare, Best, The Netherlands) system using body coil for transmission and a 32-channel head coil for receiving.

2.1 | MRF-ASL pulse sequence and dictionary matching

The details of the pulse sequence, dictionary generation, and fingerprinting matching have been described previously.²⁹ Briefly, the MRF-ASL sequence consists of varying-duration, randomly ordered control and label blocks, each followed immediately by an acquisition (Figure 1a). MRF-ASL experimental data are compared with a dictionary to find the entry that provides the best match to the measured signal time course, and the parameter values used to generate this matched entry are assigned as the estimated parameters. The dictionary is generated using simulations of perfusion kinetic models. Labeling efficiency was assumed to be 0.86, blood T_1 was 1664 msec, and blood–brain-partition coefficient was 0.9 mL/g. Two models are used in generating our MRF-ASL dictionary: one is a single-compartment model (Figure 1b), in which the imaging voxel is assumed to contain tissue only; the other one is a two-compartment model (Figure 1c), which includes an additional compartment of passing-through arterial compartment. In the single-compartment model, there are four unknown parameters in the dictionary (i.e. a four-dimensional parametric space): B_1^+ (60–110% sampled at 2% interval), tissue T_1 (500–5000 ms at 20 ms interval below 2000 ms and 300 ms interval above 2000 ms), CBF (3–150 mL/100 g/min at 3 mL/100 g/min interval), and tissue BAT (300–2000 ms at 50 interval). In the two-compartment model, there are seven unknown parameters: B_1^+ (60–110% at 3% interval), tissue T_1 (500–5000 ms at 40 ms interval below 2000 ms and 300 ms interval above 2000 ms), CBF (6–150 mL/100 g/min at 6 mL/100 g/min interval), and tissue BAT (200–2000 ms at 200 interval), pass-through arterial BAT (200–1000 ms at 200 ms interval), pass-through blood volume (0, 1–5% at 0.5% interval), and pass-through blood travel time (200–1500 ms at 200 interval). The identification of the best-match entry in the dictionary is based on the highest correlation coefficient between the simulated and experimental time courses. MRF signal in a voxel can be analyzed using both models, yielding respective parametric estimations. In this study, we

focused on the following commonly used parametric maps: 1) B_1^+ map, T_1 map, and BAT map from the single-compartment dictionary matching, as these parameters are more robust in the single-compartment results due to lower dimension of the parametric space, and 2) CBF map from the two-compartment dictionary matching, as it can account for vascular artifacts due to the inclusion of a dedicated large-vessel compartment in the model.

2.2 | Study 1: TR sequence pattern in MRF-ASL

One of the most important parameters of the MRF-ASL sequence is the TR time series, which specify the values and order of TR in the data acquisition. The TR time series determine the temporal characteristics of the MR signal time course and the extent to which different MR properties (e. g. T_1 , BAT, CBF, etc.) can be separated. An ideal TR time series is such that different MR properties have different effects on the measured MR signal time course and that the effect of each property is large enough to be distinguished from the noise. Our prior proof-of-principle report used a Perlin function based on previous papers on the general MR Fingerprinting.^{29,36} However, it may be that other temporal orders can be more advantageous. In this study we assessed the performance of MRF-ASL across different TR time series.

We tested 10 different TR sequence patterns as shown in Figure 2, with their respective histograms displayed in Supplemental Figure S1. A brief description of each pattern is as follows: pattern 1 was based on a Perlin function identical to our previous report²⁹; pattern 2 was the time reversal of pattern 1; pattern 3 was also a Perlin function but with a higher frequency³⁶; pattern 4 was based on sinusoid function; patterns 5 and 6 were based on uniform random distribution, each with a different seed; pattern 7 and 8 were based on normal random distribution, each with a different seed; pattern 9 was based on a saw-wave function; pattern 10 utilized a constant TR. While not exhaustive, these TR patterns covered a range of commonly used functional forms, and should provide us with a general insight on the selection of TR patterns in MRF-ASL. All TR patterns included 500 TRs.

2.2.1 | Numerical simulations—Numerical simulations were performed to assess the performance of TR time series. In the simulations, we consider a typical gray matter voxel with CBF = 60 ml/100 g/min, BAT = 1000 msec, T_1 = 1165 msec,³⁷ and B_1^+ = 100%. The MRF-ASL signal time course was simulated based on the TR series. This provides a noise-free data set. Gaussian noise with a mean of zero and a standard deviation of 1% of the M0 (typical in ASL MRI) was then added to the data set and dictionary matching was performed to obtain the estimated parameters. This process was repeated 10,000 times with different instances of noise. Mean and standard deviation of the estimated parameters relative to the ground truth were determined for this hypothetical voxel, and were used as an accuracy and precision index, respectively, of the particular TR time series. Simulations were repeated with other values of CBF, BAT, T_1 , and B_1^+ , so that other hypothetical voxels can be investigated.

2.2.2 | Experiments—MRF-ASL with ten TR sequence patterns was then tested *in vivo*. Imaging parameters of MRF-ASL were: the label and control schemes were pseudo-randomized but were the same for all TR patterns, no post-labeling-delay, gradient-echo 2D

EPI acquisition, voxel size = $2.8 \times 2.8 \times 10$ mm, field-of-view (FOV) = 180×180 mm, single slice, flip angle = 50° , TE = 9.3 ms, SENSE factor = 2.4, scan duration = ~3 min (ranging from 2 min 49 s to 3 min 16 s depending on the TR pattern). Additionally, a conventional, single-delay pCASL (labeling duration 1800 ms, post-labeling delay 1800 ms, scan time 4 minutes) was performed for comparison with the MRF-ASL results. In this study, 5 healthy subjects were scanned (age 31 ± 10 years old, 2 males, 3 females).

In three additional subjects (age 28 ± 6 years old, 1 males, 2 females), we performed conventional T_1 and B_1^+ mapping. The T_1 mapping sequence used the following parameters: multi-TI inversion recovery (IR) T_1 mapping sequence; TI = 180, 630, 1170, 1830, 2610, 3450, 4320, 5220, 6120, 7010 msec; recovery time [between the excitation pulse and next inversion pulse] = 8000 msec³⁷; gradient-echo 2D EPI acquisition, TE = 9.3 ms; number of signals averaged (NSA) = 1; scan time = 1 min 53 sec. The B_1^+ mapping sequence used the following parameters: Dual-TR B_1^+ mapping sequence (Actual Flip Imaging sequence)³⁸; TR = 30/150 msec; TE = 4 msec; gradient-echo 2D; NSA = 4; scan time = 47 sec. The geometric parameters of these sequences matched that of the MRF-ASL, although they were performed in a separate group of subjects. The T_1 and B_1^+ data from these subjects were averaged and served as reference parametric values for the MRF-ASL data.

2.2.3 | Data analysis—Dictionaries were generated for each TR time series using simulations of Bloch equation and perfusion kinetic models. Dictionary matching was then performed for each dataset using the corresponding dictionary to obtain parametric maps.

The quality of parametric maps was compared across TR patterns. The precision of the maps was examined by spatial correlation between the map of interest and the averaged map over all TR patterns. A higher correlation-coefficient would indicate that the map is more reproducible.

The accuracy of the maps was evaluated by comparing the parametric values to those obtained with conventional sequences. The T_1 map was segmented using FSL-FAST toolbox (University of Oxford, UK)³⁹ to obtain a gray matter mask which was applied to the T_1 and B_1^+ maps to yield region-of-interest (ROI) parametric values.

A repeated Analysis-of-variance (ANOVA) test was applied to determine if there is a significant difference across TR patterns.

2.3 | Study 2: Comparison between MRF-ASL and DSC MRI

2.3.1 | Experiments—In this study we sought to compare the MRF-ASL parametric maps with those obtained with Gd-based DSC MR Perfusion. Eight healthy subjects (26 ± 4 years old, 4 Females) were studied. A 7-slice version of the MRF-ASL sequence was used to ensure sufficient spatial overlap with the DSC scan. The 7-slice MRF-ASL sequence was similar to the single-slice sequence except that 6 additional slice excitations and acquisitions were appended to the end of the first slice acquisition. The scan used the following parameters: gradient-echo EPI acquisition, voxel size = $2.8 \times 2.8 \times 10$ mm, slice gap = 1 mm, FOV = 180×180 mm, flip angle = 40° , TE = 9.3 ms, SENSE factor = 2.4, descending slice order, the operating mode of SAR was Normal (Level 0) with whole body SAR < 0.2

W/kg and head SAR < 84% of maximum for the limiting head SAR, scan time 3 min 43 sec. The labeling duration and order were based on results from Study 1 (see Results section below), but the TR values were slightly longer due to the multi-slice acquisition used (each TR was increased by 55 ms compared to single-slice). The sequence was performed three times to improve the SNR and to provide an evaluation of test–retest reproducibility. The total scan time for three repetitions was 11 min 9 sec. The MRF-ASL scans were followed by the DSC scan which used the following sequence: gradient-echo EPI, TR = 1000 ms, TE = 30 ms, flip angle = 54°, Gd contrast agent (ProHance), dosage 0.1 mmol/kg, injection rate: 5 ml/s, voxel size = $2.8 \times 2.8 \times 5$ mm, slice gap = 0.5 mm, 18 slices, scan time 72 seconds. The scan protocol also included a T₁-weighted magnetization-prepared rapid acquisition of gradient echo sequence (T₁-MPRAGE). The scan parameters of the T₁-MPRAGE sequence were as follows: TR/TE/TI = 8.1/3.7/1100 msec, shot interval 2100 msec, flip angle 12°, voxel size $1 \times 1 \times 1$ mm³, number of slices 160, sagittal slice orientation, and duration 3 min 57 sec.

2.3.2 | Data analysis—For analysis of the multi-slice MRF-ASL data, a dictionary was generated for each slice in the scan, as different slices have slightly different labeling timing within each TR. The same dictionary was used for all subjects. Dictionary matching was performed to obtain parametric maps. Results from the three repetitions were computed for spatial correlations between repeated scans and for coefficient of variation (CoV). The DSC data were analyzed to obtain CBF, time-to-peak (TTP), and BAT maps using an FDA-approved software (Olea Sphere; Olea Medical Solutions, La Ciotat, France; Philips Healthcare, Best, The Netherlands). Arterial input function (AIF) was manually determined from a proximal location of the middle cerebral artery (MCA), either on the left or right side depending on the conspicuity of the vessel, and used for deconvolution analysis. An oSVD (oscillating index Singular Value Decomposition)⁴⁰ algorithm was used for deconvolution in the DSC data analysis, which is a delay-insensitive and semi-automatic method by iteratively repeats the block-circulant SVD (cSVD). To facilitate the comparison with BAT derived from MRF-ASL, DSC TTP and BAT were re-referenced to values in the ICA (ICA voxels were manually identified according to DSC CBV maps with 4 voxels). To enable comparison between MRF-ASL and DSC results, raw images from MRF-ASL and DSC were first coregistered to the subject's MPRAGE image, then the transformation was applied to the quantitative maps, essentially interpolating the parametric values. Next, the MPRAGE was normalized to the Montreal Neurological Institute (MNI) template. The transformation was also applied to the coregistered parametric maps to convert them into the MNI space. Group averaged parametric maps were then generated by averaging the maps in MNI space from all eight subjects. Coregistration and normalization were performed using SPM 12 (University College London, UK).

ROI analysis was based on the parcellation of MPRAGE using MRICloud (www.mricloud.org).⁴¹ MRICloud parcellates the entire brain into 53 regions. Averaged CBF and BAT values within each region were calculated for each subject. Group averaged values from all subjects were also calculated for the 53 regions. Correlation coefficient was calculated for CBF, TTP, and BAT ROI values between MRF-ASL and DSC, on both individual-level and group-level data. Whole-brain gray and white matter ROI values were

obtained by segmenting the brain using T_1 maps and applying the masks on the parametric maps.

3 | RESULTS

3.1 | Study 1: TR sequence pattern in MRF-ASL

MRF-ASL signal time courses generally follow the pattern of the TR time series (see Figure 3a for simulated MRF-ASL time courses). Simulations also verified that a change in the kinetic model parameters caused a change in the signal time course (see Figure 3b for the effects of CBF on the time course). Figure 4 summarizes results from numerical simulations on the precision and accuracy of parameter estimations. Evaluation of the precision plots (top row of Figure 4) revealed that the optimal pattern choice depends on the specific model parameters interested. For hemodynamic parameters (i.e. CBF and BAT), Pattern 4, the repeated sinusoid curve, generally manifested superior performance compared to the other patterns. Similarly, in terms of the accuracy (bottom row of Figure 4), Pattern 4 compared favorably to the other ones when it comes to CBF and BAT estimations. Pattern 10, the constant TR, showed a good accuracy of CBF estimation but its precision was poorest among all patterns tested. Similar simulation results were observed when using other assumed parametric values (Supplemental Figure S2).

Figure 5 shows MRF-ASL parametric maps from different TR sequence patterns from a representative subject, in which the B_1^+ , T_1 , and BAT maps were from the single-compartment model and the CBF maps are from the two-compartment model. Visual inspection suggested that Pattern 10, i.e. constant TR, clearly under-performed the other patterns. Results from this pattern were therefore excluded when computing averaged parametric maps (far right column in Figure 5). It can also be noted that BAT-map of pattern 5 has more artifacts than other patterns in white matter with unrealistically low arrival time, indicating poor performance of TR pattern 5 in estimating long bolus arrival time. This observation was consistent across all subjects. Figure 6 shows spatial correlations between parametric map of individual TR pattern and the averaged map. The correlation coefficients (CC) are shown for B_1^+ , T_1 , CBF, and BAT maps separately (Figures 6a–d), as well as for their average (Figure 6e). It can be seen that the optimal TR pattern depends on the parameter of interest. When examining the averaged CC values, repeated ANOVA test revealed that there was a significant difference across TR patterns ($p < 0.001$). TR Pattern 4, i.e. repeated sinusoidal function, yielded the highest overall CC value. This experimental observation that Pattern 4 appears to provide the best reliability is consistent with results from simulations (cf. Figure 4). Post-hoc analyses showed that CC of Pattern 4 was significantly greater than Patterns 1, 2, 5, and 10, but was not different from Patterns 3, 6, 7, 8 and 9. As an additional analysis, we also computed CC between different TR patterns (forming a CC matrix) and obtained an averaged CC for each pattern. The results are shown in Supplemental Figure S3, revealing similar findings as Figure 6.

Comparison between MRF-ASL CBF and that of conventional, single-delay pCASL is shown in Supplemental Figure S4 for all five subject studied. Spatial correlations between MRF-ASL and pCASL CBF maps (Supplemental Figure S5) ranged from 0.16 to 0.50, which were lower than correlations between MRF-ASL CBF maps (from 0.18 to 0.60).

To compare the accuracy of parametric estimations across TR patterns, we obtained ROI values from the gray matter and compared them to values measured from gold-standard B_1^+ and T_1 mapping sequences. Figure 7 shows the absolute differences between MRF-ASL derived parametric values and those from the gold-standard sequences. Here the lower the difference is, the better. It can also be seen that the experimental data displayed in Figure 7 are in good agreement with simulation results (cf. Figure 4e and f).

3.2 | Study 2: Comparison between MRF-ASL and DSC MRI

Since the MRF-ASL sequence was performed three times, we first report test–retest reproducibility of the data. Spatial correlation between voxel-wise parametric maps from repeated scans was 0.997 ± 0.006 (mean $\pm$ SD, $N = 8$), 0.962 ± 0.031 , 0.746 ± 0.086 , and 0.863 ± 0.054 for B_1^+ , T_1 , CBF, and BAT, respectively. CoV of the four parameters in the gray matter ROI was $0.9 \pm 0.3\%$, $1.5 \pm 0.8\%$, $9.2 \pm 5.7\%$, and $3.5 \pm 2.3\%$, respectively. For the white matter ROI, CoV was $0.8 \pm 0.2\%$, $1.1 \pm 0.9\%$, $8.9 \pm 6.5\%$, and $4.4 \pm 2.4\%$ for B_1^+ , T_1 , CBF, and BAT, respectively.

Figure 8a shows group-averaged ($N = 8$) CBF maps using MRF-ASL and DSC. It can be seen that maps obtained with MRF-ASL show excellent concordance with those from DSC. It should be noted, however, that DSC CBF is still highly dependent on the singular value threshold and SNR level even with oSVD method, thus it is possible that DSC-CBF may not reflect the true perfusion values. Images from individual subjects are shown in Supplemental Figure S6. Figure 8b displays comparisons between timing results measured with MRF-ASL and DSC. Similar to the CBF results, a spatial consistency between the two techniques is apparent. Large variations can be observed from individual DSC-BAT maps (Figure S6), while MRF-BAT is more comparable across subjects, suggesting that MRF-ASL can assess BAT more reliably than DSC.

Certain differences between the maps can also be seen. For CBF, venous signal is more prominent in the DSC CBF map than in the MRF-ASL map (green arrows in Figure 8a). This is because Gd contrast agent is an intravascular agent and does not diffuse through capillary. Thus the effects of Gd are also present in veins even though such effects do not represent true perfusion. For the timing parameters, the value range of DSC TTP and BAT is generally larger than that of MRF-ASL BAT (see blue arrows in Figure 8b). This is partly due to venous effects in DSC (i.e. veins have a longer TTP and BAT) but also because MRF-ASL uses a short half-life tracer (i.e. T_1 of blood is only 1.5–2 s at 3 T). Thus its ability to estimate BAT longer than 4 seconds may be limited, and may result in an under-estimation. This is most obvious in the major veins and ventricle regions. Table 1 summarizes quantitative CBF BAT values obtained with the two techniques.

Figures 8c and 8d show scatter plots between group-averaged ROI values measured with MRF-ASL and DSC MRI, which correspond to correlation coefficient of 0.79, 0.91, and 0.91 for CBF, TTP, and BAT, respectively. Similar analyses of individual-level ROI data resulted in correlation coefficients of 0.69 ± 0.06 (mean $\pm$ SD, $N = 8$), 0.84 ± 0.07 , and 0.83 ± 0.08 for CBF, TTP, and BAT, respectively.

Voxel-wise comparison between MRF-ASL and DSC maps confirmed the ROI results (Supplemental Figure S7). The most prominent differences are seen in the absolute BAT/TTP maps, in that absolute BAT/TTP obtained from DSC is longer than that from MRF-ASL throughout the brain. In the relative maps, on the other hand, negligible differences are seen.

4 | DISCUSSION

MR Fingerprinting represents an interesting approach in the MR field, in which the complexity of MR signal mechanism is exploited for simultaneous and quantitative estimation of multiple parameters. Due to the fact that ASL signal is dependent on the interplay of several hemodynamic and MR parameters, ASL may be an excellent application of the MRF framework. While a proof-of-principle of MRF-ASL was reported previously,²⁹ limited consideration was given to sequence parameter selections. Furthermore, the prior study did not compare MRF-ASL with Gd-based perfusion MRI, which is the current standard in clinical MRI. In this study, we examined the dependence of MRF-ASL data on a key sequence parameter, TR pattern. The results revealed that there was a significance dependence of the sequence performance on TR pattern, although there was not a single pattern that provided dramatically improvements. Among the TR patterns tested, a sinusoidal pattern with a period of 125 TRs provided an overall best estimation in terms of spatial consistency. We also compared the MRF-ASL derived hemodynamic maps with Gd-based DSC MRI. The results showed that these two methods provided visually consistent and quantitatively correlated estimations of CBF and BAT results, notwithstanding some differences in absolute values and discrepancies in major veins and ventricular regions.

In MR Fingerprinting sequences, the TR, TE, or flip angle are intentionally varied with time, thus producing a non-steady-state signal time course. As a result, the series defining this time-dependent pattern is the most important parameter in MRF. For the MRF-ASL sequence investigated in this study, it corresponds to the TR time series, as TE and flip angle were not varied in our sequence. It is reasonable to expect that some patterns outperform others in the estimation of target parameters. Optimal design of MR Fingerprinting time series remains an active area of research in the field.^{42–44} In our study, we used both experimental and simulation approaches to compare the performance of different TR patterns. Although not an exhaustive list, our study of 10 TR patterns revealed some general insights on the choice of TR pattern in MRF-ASL. First, there does not appear to be a “silver bullet” TR pattern that can provide a drastic improvement in SNR compared to the TR pattern used in the previous study. Additionally, it seems that a few TR patterns should be avoided due to their poor performance. For example, the constant TR pattern, Pattern 10, performed the worst among all patterns tested. Also, uniform and normal random distribution, i.e. Pattern 5 through 8, performed poorly in the estimation of T_1 because of limited dynamic range of the signal (as shown in Supplemental Figure 3a).

Although ASL MRI is a non-invasive CBF technique that has been increasingly used in neurological and psychiatric diseases,^{1,3–7,45,46} its application in cerebrovascular diseases has not been widely embraced in the clinical diagnostic setting.^{24,25} One possible reason is that patients with cerebrovascular diseases often have altered BAT, which may confound the

measurement of CBF using ASL. Another possibility is that BAT itself may be a sensitive marker in cerebrovascular diseases. Regardless the exact reason, MRF-ASL may be useful in such diseases because it is capable of assessing multiple hemodynamic parameters simultaneously, in particular teasing apart the effects of BAT and CBF. In our study, we compared MRF-ASL with contrast based MR perfusion in young healthy subjects, and the results showed that these two methods provided highly comparable CBF and BAT estimations. Therefore, future studies should explore the potential of MRF-ASL in cerebrovascular diseases, such as stroke, atherosclerosis, and moyamoya disease, particularly when Gd administration is contraindicated, e.g. in cases of low glomerular filtration ratio (GFR), allergy to contrast agent, difficulties with intravenous line placement, or concerns of Gd deposition in the brain after repeated use.

Test–retest reproducibility of the MRF-ASL using sinusoidal TR pattern was evaluated. Compared to reports in the literature (see a summary in Table 2), the CoV values obtained from MRF-ASL are comparable to those using other ASL methods.^{18,23,47–51} It should be noted that the scan time of MRF-ASL is among the shortest of the studies in Table 2. We also want to point out that our CBF estimation was based on a two-compartment model that separately considers tissue and vessel ASL signals. When evaluating CBF results from a single-compartment model, which was the model used in most of the previous reports, CoV of our gray matter and white matter CBF results reduced to $5.1 \pm 3.4\%$ and $6.3 \pm 4.7\%$, respectively.

One limitation of our current implementation of MRF-ASL is the high computation cost in terms of processing time and storage space. For example, in the present study, a Linux cluster server and parallel computing were used for dictionary matching and the processing time for a multi-slice dataset was approximately 2 hours. Computation burden may therefore limit the application of our sequence in acute clinical settings such as stroke. However, we note that computer technologies are evolving rapidly and it can be expected that the computation time will be substantially shortened in the future. Additionally, several approaches can be used to further address this problem.^{52–56} One approach is to compress the dictionary using the singular value decomposition (SVD), which provides a low-rank approximation of the dictionary to save disk space and accelerate the dictionary matching.^{53,54} Other promising methods include applying deep learning and neural networks in MRF to reduce memory cost and increase the speed of pattern recognition.^{55,57–59} Another limitation of this study is that, while we tested the impact of TR pattern on MRF-ASL results, the ordering of control and label TRs was based on a single-instance random-number generator but was not systematically studied. Therefore it is possible that a different control/label order would provide more superior sensitivity. Also, we only tested a limited number of TR patterns due to scan time constraints and not all features or considerations of the temporal pattern were studied. A final limitation is that kinetics of perfusion is a complex phenomenon, and the models used in this work made a number of assumptions and are still an over-simplification of the true effects. To put this discussion in the context of literature, the kinetic model used in the recent ASL white paper was the simplest form and assumed that tissue T_1 equals blood T_1 and that the bolus arrival time is shorter than the post-labeling delay. The “single-compartment” model employed in the present work is already an expansion of the white-paper model by allowing tissue T_1 and bolus arrival time to be

variables. The “two-compartment” model is a further expansion by adding a separate arterial compartment, the blood of which is destined to perfuse tissue outside the current voxel. This expansion added several other parameters such as arterial compartment volume fraction, arterial compartment arrival time, and travel time. We can in principle develop a more sophisticated model by accounting for factors such as pulsatile flow, labeling bolus dispersion, and labeling efficiency. However, the inclusion of more parameters will result in the fitting procedure becoming less reliable. Therefore, we had to identify a tradeoff by making certain assumptions on these factors.

5 | CONCLUSION

In this study, the dependence of MRF-ASL sequence performance on TR pattern was investigated. It was found that the performance of MRF-ASL varied with TR patterns, but not a single pattern could provide superior results for all parameters estimated. For CBF and BAT estimations, a sinusoidal pattern with a period of 125 TRs provided an overall best estimation among the TR patterns tested. Comparison between MRF-ASL and DSC MRI revealed that the two techniques showed qualitative concordance, although some differences were still present, particularly in the timing maps. MRF-ASL is a promising alternative technique to Gd-based perfusion MRI for non-invasive, multi-parametric perfusion assessment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ADHD	Attention-Deficit/Hyperactivity Disorder
AIF	Arterial Input Function
ANOVA	Analysis of Variance
ASL	Arterial Spin Labeling
BAT	Bolus Arrival Time
CBF	Cerebral Blood Flow

CBV	Cerebral Blood Volume
CC	Correlation Coefficient
CoV	Coefficient of Variation
DSC	Dynamic Susceptibility Contrast
ICA	Internal Carotid Artery
MCA	Middle Cerebral Artery
MNI	Montreal Neurologic Institute
MRF	Magnetic Resonance Fingerprinting
oSVD	oscillating index Singular Value Decomposition
pCASL	Pseudo-Continuous ASL
PLD	Post Labeling Delay
ROI	Region of Interest
TTP	Time to Peak

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FIGURE 1.

Pulse sequence and kinetic models of MRF-ASL. a) Schematic diagram of the MRFASL pulse sequence. The sequence consists of varying duration, randomly ordered control and label pCASL modules, each followed immediately by an acquisition; b) single-compartment model. The imaging voxel is assumed to contain tissue only; c) two-compartment model. The voxel contains an additional compartment of passing-through arterial compartment

FIGURE 2.

Ten different TR sequence patterns tested in this study. Pattern 1 was based on a Perlin function identical to our previous report; pattern 2 was the time reversal of pattern 1; pattern 3 was also a Perlin function but with a higher frequency; pattern 4 was based on sinusoid function; patterns 5 and 6 were based on uniform random distribution, each with a different seed; pattern 7 and 8 were based on normal random distribution, each with a different seed; pattern 9 was based on a saw-wave function; pattern 10 utilized a constant TR (so that labeling duration is the midpoint between minimal and maximal labeling duration). All TR patterns included 500 TRs

FIGURE 3.

Representative simulation results. a) Simulated MRF-ASL signal time courses in a representative gray matter voxel for all the TR series (CBF = 60 ml/100 g/min, BAT = 1000 msec, $T_1 = 1165$ msec and $B_1^+ = 100\%$). b) the effects of CBF on the time courses, which is the difference between the signal time course from the typical gray matter voxel with perfusion (CBF = 60 ml/100 g/min) and the signal time course from a hypothetical gray matter voxel without perfusion (CBF = 0 ml/100 g/min)

FIGURE 4.

Results from the numerical simulations. Top row: Precision; bottom row: Accuracy. The precision index is calculated as the standard deviation of difference (between the ground-truth value and the estimated value) across multiple trials. The accuracy index is calculated as the absolute difference between the ground-truth value and the mean estimated value

FIGURE 5.

MRF-ASL results from a representative subject using the 10 TR sequence patterns. Far right column: Averaged parametric maps across pattern 1–9 (results from pattern 10 was excluded when computing averaged maps as it clearly under-performed the other patterns)

FIGURE 6.

Spatial correlations between parametric map of individual TR pattern and the averaged map. The correlation coefficients (CC) are shown for B_1^+ , T_1 , CBF, and BAT maps separately, as well as for their average

FIGURE 7.
Absolute difference between ROI values of B_1^+ and T_1 from the gray matter and the values measured from conventional B_1^+ and T_1 mapping sequences

FIGURE 8.

Comparison between MRF-ASL and DSC MRI results ($N = 8$). (a) Comparison of CBF maps. Parametric maps were calculated for each subject and then averaged across subjects. (b) Comparison between BAT map obtained with MRF-ASL and BAT/TTP maps obtained with DSC MRI. (c, d) scatter plots of ROI values between the two methods. ROIs were delineated using an automatic parcellation tool from MRI cloud. Each dot in the plot represents data from one ROI. p values for all three correlations are below 0.000001

TABLE 1

Summary of gray and white matter CBF and BAT using different techniques

	MRF-CBF (ml/100 g/min)	DSC-CBF (ml/100 g/min)	MRF-BAT (sec)	DSC-TTP (sec)	DSC-BAT (sec)
GM	38.3 ± 1.5	35.9 ± 1.9	0.90 ± 0.03	2.00 ± 0.14	1.95 ± 0.17
WM	27.1 ± 1.1	20.5 ± 1.2	1.18 ± 0.04	2.73 ± 0.17	2.53 ± 0.18

TABLE 2

Comparison of reproducibility between MRF-ASL and literature studies

Reproducibility of CBF							
Reference	Sequence	Field	Scanner	Scan duration	Intra or inter session	Time interval	CoV
Parkes et al. 2004 ⁴⁷	CASL	1.5 T	GE	9 min	Intra	20 min	GM 2.6% WM 3.5%
Yen et al. 2002 ⁴⁸	FAIR	1.5 T	GE	8:2 min	Inter	1–4 weeks	10.7% 14.4%
Petersen et al. 2010 ²³	QUASAR	3 T	Philips	5:52 min	Intra		6.5%
Chen et al. 2011 ⁴⁹	pCASL	3 T	Siemens	5:20 min	Intra		3.5% 7.5% 4.1% 4.8%
Mutsaerts et al. 2015 ⁵⁰	pCASL	3 T	Vendor A	11:12 min/10:58 min	Inter	2:09 h ± 0:09/1:37 h ± 0:18	15.9%/9.1%
			Vendor B	11:12 min	Inter	2:10 h ± 0:12	15.40%
			Vendor C	10:58 min	Inter	1:31 h ± 0:20	8.20%
This study	MRF-ASL	3 T	Philips	3:43 min	Intra	0/3:43 min	9.2% 8.9%
Reproducibility of BAT							
Reference	Sequence	Field	Scanner	Scan duration	Intra or inter session	Time interval	CoV
Petersen et al. 2010 ²³	QUASAR	3 T	Philips	5:52 min	Intra		5.6%
Guo et al. 2018 ¹⁸	5-PLD pCASL	3 T	GE	4:50 min	Intra	15 min	23.3%
	7-PLD Hadamard			4:25 min	Intra	15 min	17.0%
Sousa et al. 2014 ⁵¹	PICORE	3 T	GE	7:20 min	Inter	1 week	3–13%
This study	MRF-ASL	3 T	Philips	3:43 min	Intra	0/3:43 min	3.5% 4.4%