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Fast Magnetic Resonance Fingerprinting for Dynamic Contrast-Enhanced Studies in Mice

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Abstract

Purpose—The goal of this study was to develop a fast magnetic resonance fingerprinting (MRF) method for simultaneous T_1 and T_2 mapping in dynamic contrast-enhanced MRI studies in mice.

Methods—MRF sequences based on balanced steady-state free precession (bSSFP) and fast imaging with steady-state precession (FISP) were implemented and evaluated on a 7T preclinical scanner. The readout used a zeroth-moment compensated variable density spiral trajectory that fully sampled the entire k-space and the inner 10×10 k-space with 48 and 4 interleaves, respectively. *In vitro* and *in vivo* studies of mouse brain were performed to evaluate the accuracy of MRF measurements with both fully- and under-sampled data. The application of MRF to dynamic T_1 and T_2 mapping in DCE-MRI studies were demonstrated in a mouse model of heterotopic glioblastoma using gadolinium- and dysprosium-based contrast agents.

Results— T_1 and T_2 measurements in phantom showed strong agreement between the MRF and the conventional methods. MRF with spiral encoding allowed up to 8-fold undersampling without loss of measurement accuracy. This enabled simultaneous T_1 and T_2 mapping with 2-min temporal resolution in DCE-MRI studies.

Conclusion—MRF provides the opportunity for dynamic quantification of contrast agent distribution in preclinical tumor models on high-field MRI scanners.

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Keywords

MR fingerprinting; gadolinium; dysprosium; dynamic contrast-enhanced MRI; mouse

Introduction

Quantification of contrast agent uptake and distribution in dynamic contrast-enhanced MRI (DCE-MRI) have shown high sensitivity and specificity to many pathological changes (1–3). The linear relationship between relaxation rate (R_1 and R_2) and contrast agent concentration enables the quantification of contrast agent uptake by measuring changes in T_1 and/or T_2 relaxation times (4). Simultaneous quantification of T_1 and T_2 also provides the opportunity to detect two contrast agents with a single injection (5). However, conventional methods of T_1 and T_2 mapping that rely on curve fitting to relaxation models require long acquisition time. The low temporal resolution is thus not adequate for DCE-MRI studies. Although several methods have been developed that can accelerate data acquisition by sampling multiple points along a relaxation curve during each excitation, very few methods can provide simultaneous T_1 and T_2 mapping with sufficiently high temporal resolution (6–9). The requirement of high spatial resolution for T_1 and T_2 mapping in mouse poses further limitation on the temporal resolution.

Magnetic resonance fingerprinting (MRF) is a novel quantitative imaging method that allows simultaneous, multi-parametric mapping with high acquisition efficiency (10,11). In addition, MRF has also demonstrated great tolerance to under-sampling errors, which provides the opportunity for dynamic quantification of contrast agent accumulation in DCE-MRI studies with high spatial and temporal resolution. Since its invention, various MRF methods have been developed for efficient, multi-parametric mapping in the brain (12,13), liver (14), myocardium (15), and prostate (16). Recently, Wang et al also developed a phosphorous-31 MRF spectroscopic method for efficient quantification of metabolic activity in skeletal muscle (17).

MRF sequences based on balanced steady-state free precession (bSSFP) or fast imaging with steady-state precession (FISP) have been developed for clinical applications (10,11). Although bSSFP-based MRF shows higher efficiency, the accuracy of the measurements can be affected by banding artifacts resulting from field inhomogeneity (11). On the other hand, FISP-based MRF is largely immune to the banding artifacts at the cost of slightly compromised efficiency. Previously, we developed a FISP-based MRF sequence on a 7T preclinical scanner (18). Although the use of Cartesian trajectory in that implementation did not take advantage of the high under-sampling capacity of MRF, our results suggest that MRF can also provide effective motion artifact suppression in T_1 and T_2 mapping in small laboratory animals.

The objective of this study was to develop a fast MRF method for DCE-MRF studies in mice. bSSFP-MRF and FISP-MRF sequences using spiral trajectories were developed on a 7T preclinical scanner. The under-sampling capacity of the two sequences were evaluated both *in vitro* and *in vivo*. Validation studies were performed to compare MRF measurements with those by conventional T_1 and T_2 mapping methods. Finally, simultaneous, dynamic T_1

and T_2 mapping in DCE-MRI studies were demonstrated in a mouse model of heterotopic glioblastoma.

Methods

Pulse Sequence and Trajectory Design

Schematics of the MRF pulse sequences are shown in Figure 1a. An adiabatic inversion pulse was applied at the beginning of the sequence to enhance T_1 sensitivity. The subsequent fingerprint acquisition consisted of four segments (Figure 1b). In each of the first three segments, Flip angle (FA) was sinusoidally ramped up and then ramped down across a total of 250 acquired frames. In the last segment, FA was sinusoidally ramped up, and only 124 frames were acquired. The maximal FA in odd and even segments was set to 50° and 25° , respectively. Random variation with a standard deviation of 5° was added to the sinusoidal profile. Each segment was followed by 50 frames with 0° FA to allow partial relaxation. A total of 1024 frames were acquired. Excitation used a 7-lobe sinc pulse to ensure a satisfactory slice profile. The phase of the excitation pulses alternated between 0° and 180° to place the on-resonance frequency at the center of the passband of bSSFP-MRF sequence. Finally, randomized repetition time (TR) varying from 9.5 to 12.2 ms was selected from a Perlin noise distribution for all 1024 frames (19). Total acquisition time was approximately 12 s.

Data acquisition used a variable density spiral trajectory with zeroth-moment compensation (Figure 1c). The trajectory was designed according to the method proposed by Kim et al (20), with a field of view (FOV) of $3 \times 3 \text{ cm}^2$ and a matrix size of 128×128 . 48 interleaves were used to fully sample the entire k-space, while 4 interleaves were required to fully sample the inner 10×10 k-space. Each interleaf sampled 1000 data points with a dwell time of 5 μs , yielding a 5-ms readout time. The FISP-MRF sequence used spoil gradients along the readout direction to achieve a dephasing of 2π across each pixel. To reduce eddy currents, the maximal gradient strength and slew rate were limited to 100 mT/m and 1000 T/m/s, respectively, corresponding to 25% and 50% of the hardware limitations. During data acquisition, the spiral trajectory was rotated by 7.5° from one frame to the next. The acquisition was repeated 48 times to allow complete sampling of the k-space for each time frame. A 9-s delay was inserted between each repetition to prevent excessive gradient-induced heating.

Dictionaries and Fingerprint Matching

Dictionaries for bSSFP-MRF and FISP-MRF were generated by solving the Bloch equation with designed FAs and TRs. For the simulation of a FISP-MRF fingerprint, signals from 80 spins with dephasing evenly distributed from $-\pi$ to $+\pi$ were simulated and averaged. Both dictionaries used the same set of T_1 and T_2 values that covered the ranges reported in the literature (21). Specifically, T_1 varied from 100 ms to 4000 ms with an increment of 5% per step, while T_2 varied from 5 ms to 400 ms with an increment of 5% per step. The off-resonance frequency in bSSFP-MRF dictionary varied from -80 to $+80$ Hz in 1 Hz increment. There was a total of 7,007 and 1,128,127 entries in FISP-MRF and bSSFP-MRF dictionaries, respectively.

Matching was performed by calculating the inner product between the measured and normalized fingerprint and all normalized dictionary entries. The normalized dictionary entry producing the largest inner product was taken to represent the closest match. T_1 and T_2 values were derived from the matched entry, as well as the off-resonance frequency for bSSFP-MRF sequence. Spin density was then calculated as the scaling factor between measured signal and the matched dictionary entry without normalization.

In Vitro Validation

All MRI studies were performed on a horizontal 7T Bruker Biospec scanner (Bruker Biospin Co., Billerica, MA) using a 35-mm birdcage coil. A ten-compartment phantom, consisting of manganese chloride (Mn^{2+}) dissolved in distilled water at concentrations ranging from 50 μM to 500 μM , was used for *in vitro* validation. Data was acquired from a single axial slice using both bSSFP-MRF and FISP-MRF sequences. Imaging parameters were: slice thickness, 1.5 mm; FOV: $3 \times 3 \text{ cm}^2$; matrix size: 128×128 . These parameters gave rise to an in-plane resolution of $0.23 \times 0.23 \text{ mm}^2$. Acquisition time was 21 s for each interleaved, or approximately 17 min per slice for fully sampled data with 48 interleaves.

To evaluate the under-sampling capacity of the MRF sequences, the fully-sampled datasets were retrospectively under-sampled with an under-sampling factor of 2, 3, 4, 6, 8, 12, 16, 24, and 48, respectively. All image frames were reconstructed using the non-uniform fast Fourier transform (NUFFT) toolbox (22). Density compensation was applied prior to regridding (23). Subsequently, T_1 , T_2 , and off-resonance (for bSSFP-MRF only) maps were generated from dictionary matching. Parameter estimation from under-sampled data was compared with that from fully sampled data by calculating the normalized root mean square errors (NRMSE). Pixel-wise comparison was also performed using linear regression and residual maps.

A validation study was performed to compare MRF with conventional T_1 and T_2 mapping methods. Due to the high gradient duty cycle of the MRF experiments, significant temperature increase of approximately $5.6^\circ C$ was observed during the acquisition of fully-sampled MRF dataset from a temperature probe placed on the surface of the phantom. This temperature increase led to significant changes in T_1 and T_2 of the phantoms. To maintain constant T_1 and T_2 during data acquisition, MRF data were acquired with an under-sampling factor of 8 and 16, respectively. For comparison, saturation recovery Look-Locker (SRLL) sequence was used for T_1 mapping (24), and multi-slice multi-echo (MSME) sequence was used for T_2 mapping. T_1 mapping by SRLL acquired 50 images at 120-ms interval and with a 10° FA after saturation. An M_0 image was acquired with the same FA and 2000-ms TR. The total acquisition time was approximately 6.4 min. T_2 mapping by MSME used a TR of 1000 ms with TE varying from 8 to 512 ms at an increment of 8 ms. Total acquisition time was approximately 2 min.

In Vivo Experiments

In vivo studies were performed on 4-month male C57BL/6 mice and female tumor-bearing athymic nude mice. The animal protocol was approved by the Institutional Animal Care and Use Committee of the Case Western Reserve University. Anesthesia was induced with 2%

isoflurane mixed with 100% oxygen in an induction chamber, and was maintained with 0.5 to 1% isoflurane mixed with 100% oxygen delivered via a nosecone. The mouse was placed in the cradle in a prone position. Respiration rate and body temperature were monitored during the experiments. The respiration rate was maintained within 80 to 100 breaths per minute (bpm) by adjusting the anesthesia level. The body temperature was maintained at approximately 35°C by blowing warm air into the magnet through a feedback control system (SA Instruments, Stony Brook, NY).

T₁ and T₂ maps were acquired from an axial slice of the brain of C57BL/6 mice (n=3) using both the MRF and the conventional T₁ and T₂ mapping methods. For MRF acquisition, both fully- and under-sampled data (R=8 and 16) were acquired. Due to the effects of anesthesia and systemic circulation, body temperature did not change significantly during the acquisition of MRF data. For comparison, T₁ and T₂ maps of the same axial slice were also acquired using the conventional SRLL and MSME methods as described in the previous section.

Athymic nude mice (n=5) were implanted with human LN-229 glioblastoma cells within the right flank (25). DCE-MRI studies were performed 3 weeks after tumor implant. Mice were randomly selected to receive a bolus injection of either gadolinium-based (Optimark™, n=2) or dysprosium-based (Dy-DOTA-azide, n=3) contrast agent via the tail vein. MRF acquisition used the FISP-MRF sequence with an under-sampling factor of 8 (6 interleaves), yielding a 2-min temporal resolution. A total of 5 (10-min acquisition) and 10 datasets (20-min acquisition) were acquired at the baseline and after injection, respectively.

Statistics

All results are presented as mean ± standard deviation. Linear regression and Lin's concordance correlation coefficient (CCC) were used to compare results using under-sampled MRF data with that from fully-sampled MRF data, as well as to compare MRF with conventional methods in phantom studies (26). Paired Student t-test was used to compare the MRF measurements with the conventional methods, as well as to compare measurements obtained using under-sampled MRF data with that from fully-sampled data in brain and CSF. Significant difference was accepted at P<0.05.

Results

Phantom Results – Under-sampling Capacity

Figure 2 shows reconstructed images, representative fingerprints, and parameter maps from fully-sampled FISP-MRF data and retrospectively under-sampled data with under-sampling factors (R) of 4, 8, and 16, respectively. Results from bSSFP-MRF data are shown in Figure S1. With a high under-sampling factor (R=8 and 16), the aliasing artifacts became dominant in the reconstructed images, with increased aliasing noise in the fingerprints. However, T₁ and T₂ maps were similar to those generated from the fully-sampled data. NRMSE of T₁ and T₂ maps generated from under-sampled data and pixel-wise comparisons of T₁ and T₂ estimation between fully- and under-sampled (R=8 and 16) FISP-MRF and bSSFP-MRF data are shown in Figures 3 and S2, respectively. In general, NRMSE increased only slightly

when R increased from 2 to 16. Both methods showed similar NRMSE for T_1 estimation, while NRMSE of T_2 maps was an order of magnitude higher for bSSFP-MRF with an under-sampling factor of 48. T_1 estimation showed great tolerance to under-sampling errors for both bSSFP-MRF and FISP-MRF, with a CCC greater than 0.99. At R=16, T_1 values calculated from under-sampled data showed strong agreement with that from the fully-sampled data, with >97% of the pixels showed a difference within two dictionary steps (<10% error). FISP-MRF also demonstrated accurate T_2 mapping with <10% error for 90% of the pixels at R=16, while T_2 estimation by bSSFP-MRF showed more discrepancies with only 67% of the pixels showed an error of <10%.

Phantom Results – Validation by Conventional Methods

Comparisons of T_1 and T_2 measurements by MRF and conventional methods are shown in Figure 4 for FISP-MRF and Figure S3 for bSSFP-MRF. For both MRF methods, mean T_1 values in all ten compartments showed strong agreement with that measured by SRLL, with a CCC greater than 0.98. MRF measurements showed a smaller standard deviation than SRLL measurements, suggesting more consistent T_1 estimation by MRF methods. For T_2 estimation, there was a slight decrease in CCC that was primarily caused by discrepancies in the estimation of short- T_2 species. MRF measurements at R=16 exhibited comparable performance to that at R=8 for both methods, albeit with only half the scan time.

In Vivo Results – T_1 and T_2 Mapping in Mouse Brain

Representative T_1 and T_2 maps of a mouse brain are shown in Figure 5a. Comparison of mean T_1 and T_2 values in regions of interest (ROI) representative of cerebrospinal fluid (CSF) and brain are shown in Figure 5b. T_1 estimation by both MRF methods showed good agreement with the SRLL method. No significant differences in mean T_1 values were observed in both CSF and brain. T_1 estimation with under-sampled data (R=8 and 16) was also similar. T_2 measurement by bSSFP-MRF showed large variations in CSF, while FISP-MRF showed more consistent T_2 measurements with both fully sampled and under-sampled data (R=8 and 16). However, mean T_2 values in brain were lower than that by MSME method.

In Vivo Results – Application to DCE-MRI Studies

Shown in Figures 6 and 7 are results from two DCE-MRI studies on mice injected with gadolinium- and dysprosium-based contrast agent, respectively. Gadolinium-based contrast agent induced significant T_1 reduction and relatively unaltered T_2 (Figure 6a). On the other hand, dysprosium-based contrast agent induced more pronounced T_2 reduction but only a slight decrease in T_1 (Figure 7a). On average, gadolinium-based contrast agent induced a 54% reduction in T_1 , while dysprosium-based contrast agent induced a 43% reduction in T_2 . Shown in Figures 6b and 7b are dynamic changes in relaxation rates (R_1 and R_2) from regions at the core and periphery of the tumor. Comparing to the periphery, the core showed slower uptake and a low peak uptake of the contrast agent, suggesting compromised perfusion.

Discussion

In the current study, we implemented and evaluated two MRF sequences, bSSFP-MRF and FISP-MRF, for fast and simultaneous T_1 and T_2 mapping in small laboratory animals at high field. Consistent with findings on the clinical scanner (11), our results show that FISP-MRF yielded more consistent T_1 and T_2 estimation both *in vitro* and *in vivo*. The results from phantom and mouse brain also demonstrate that accurate T_1 mapping can be achieved with an under-sampling factor of 16 (1-min acquisition). While T_2 mapping by MRF also showed good agreement with the conventional MSME method in phantoms, an under-estimation by MRF was observed *in vivo* in mouse brain. Despite the discrepancies, MRF demonstrated consistent T_2 mapping with an under-sampling factor of up to 16. Further, results from DCE-MRI studies suggest that the FISP-MRF method is sensitive to the T_2 -shortening effects induced by dysprosium-based contrast agent.

Previous studies on clinical scanners have demonstrated MRF's high tolerance to under-sampling errors using spiral (10,11) or radial (27) trajectories. In the initial MRF study by Ma et al (10), accurate T_1 and T_2 mapping were achieved using data from only 1 spiral interleaf that fully sampled the center 10×10 k-space, an under-sampling factor of 48. Using a multi-slice, plug-and-play MRF sequence with radial encoding, Cloos et al were able to achieve an under-sampling factor of 84 at 7T (27). Prior preclinical studies that focused on demonstrating the efficacy of MRF in imaging small animals have used Cartesian readout (18,28). These studies did not take advantage of the under-sampling capacity of MRF for efficient parameter quantification. With a typical scan time of ~25 min, MRF with Cartesian encoding is not adequate for DCE-MRI studies. In the current study, spiral trajectories that covered the center 10×10 k-space with 4 interleaves were used to maintain gradient stability, as the high spatial resolution required for mouse imaging and the high duty cycle of an MRF sequence demanded high gradient performance. Our results show that accurate T_1 mapping can be achieved with $1/16^{\text{th}}$ of the data, while consistent T_2 mapping can be achieved with $1/8^{\text{th}}$ of the data. This under-sampling capacity led to the 2-min temporal resolution in the DCE-MRI studies. With improved gradient performance, spiral trajectory that covers center 10×10 k-space with 1 interleaf can be used (10), which will lead to further improvement in temporal resolution by 6 fold.

To date, most preclinical DCE-MRI studies have relied on T_1 -weighted methods to achieve satisfactory temporal resolution (29,30). While a few studies have used variable flip angles (31) or saturation-recovery Look-Locker (32) approaches for fast T_1 mapping, simultaneous T_1 and T_2 mapping with adequate temporal resolution has not been possible in preclinical studies. In this study we demonstrated, for the first time, the utility of MRF for fast, simultaneous T_1 and T_2 mapping in DCE-MRI studies employing preclinical tumor models. The two contrast agents used in this study possess very different relaxation properties. Unlike gadolinium that is primarily a T_1 shortening agent, the major effect of dysprosium is reduced T_2 relaxation time (33). Indeed, our DCE-MRF results reflect the different relaxation properties of these two contrast agents. With simultaneous T_1 and T_2 mapping enabled by MRF, the combined use of these two contrast agents provides the opportunity for simultaneous tracking of two imaging biomarkers in molecular imaging (5).

T₁ measurement by MRF showed good agreement with that by conventional SLL method in the current study. However, an under-estimation of T₂ by MRF was observed *in vivo*. One possible cause of such under-estimation could be the effect of blood flow, as the under-estimation is more pronounced in brain tissue than in CSF. Although the underlying mechanisms of this under-estimation is not completely understood, our DCE-MRI results suggest that MRF is sensitive to the reduction in T₂ induced by dysprosium, suggesting the feasibility of using MRF to track T₂-shortening contrast agents such as manganese and dysprosium. Future works could focus on elucidating the physiological parameters that may impact T₂ measurement by MRF. Furthermore, sequence optimization with a focus on improving T₂ sensitivity and accuracy is also desirable, especially for short T₂ species.

In conclusion, we demonstrated in the current study the use of MRF method for fast and simultaneous T₁ and T₂ mapping in laboratory animals at high field. The FISP-MRF sequence enabled dynamic tracking of contrast agents in DCE-MRI studies employing mouse models of heterotopic tumors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. MRF sequences

a: MRF sequences based on bSSFP and FISP. bSSFP-MRF sequence is shown in solid lines. Dashed lines indicate dephasing gradients in FISP-MRF sequence. **b:** Flip angles and repetition times used in the acquisition of 1024 frames. **c:** One interleaf of a variable density spiral trajectory.

Figure 2. T_1 and T_2 mapping from under-sampled FISP-MRF data

a: Images of the 40th frame reconstructed from fully- ($R=1$) and under-sampled data ($R=4, 8$, and 16). **b:** Corresponding fingerprints and matched dictionary entries from the pixel highlighted in red. **c:** T_1 maps (top row) and the difference maps (bottom row) between the fully- and under-sampled results. **d:** T_2 maps (top row) and the difference maps (bottom row) between fully- and under-sampled results.

Figure 3. Comparison of T_1 and T_2 estimation from under-sampled FISP-MRF data
a: NRMSE of T_1 and T_2 estimation with different under-sampling factors (R). **b,c:** Pixel-wise correlation of T_1 and T_2 estimation between fully- and under-sampled data with an R of 8 and 16, respectively. Colors indicate data from different compartments. Lines and equations are results from linear regression. CCC: Lin's concordance correlation coefficient.

Figure 4. *In vitro* validation of FISP-MRF measurements

a: T₁ and T₂ maps acquired with conventional and FISP-MRF methods with an under-sampling factor of 8 and 16. **b,c:** Correlation between MRF measurements and the standards. Dashed lines and equations are results from linear regression. Each data point represents measurements from a compartment. Error bars represent standard deviations in corresponding compartments (about 250 to 370 pixels). CCC: Lin's concordance correlation coefficient.

Figure 5. *In vivo* results

a T₁ and T₂ maps of a mouse brain acquired with conventional and MRF methods. **b**: comparison of T₁ and T₂ measurements in ROIs representative of CSF and brain tissue. ROIs are indicated in **a**. Error bars represent standard deviations in corresponding ROIs.

Figure 6. Dynamic tracking of gadolinium distribution in heterotopic tumors by MRF
a: T₁ and T₂ maps at baseline, 4 and 18 min after gadolinium injection. **b:** Dynamic changes in R₁ and R₂ from ROIs (indicated in **a**) located at the periphery and core of tumor, respectively.

Figure 7. Dynamic tracking of dysprosium distribution in heterotopic tumors by MRF
a: T₁ and T₂ maps at baseline, 4 and 18 min after dysprosium injection. **b:** Dynamic changes in R₁ and R₂ from ROIs (indicated in **a**) located at the periphery and core of tumor, respectively.