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Preclinical Magnetic Resonance Fingerprinting (MRF) at 7 T: Effective Quantitative Imaging for Rodent Disease Models

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Abstract

High field, preclinical magnetic resonance imaging (MRI) scanners are now commonly used to quantitatively assess disease status and efficacy of novel therapies in a wide variety of rodent models. Unfortunately, conventional MRI methods are highly susceptible to respiratory and cardiac motion artifacts resulting in potentially inaccurate and misleading data. We have developed an initial preclinical, 7.0 T MRI implementation of the highly novel Magnetic Resonance Fingerprinting (MRF) methodology that has been previously described for clinical imaging applications. The MRF technology combines *a priori* variation in the MRI acquisition parameters with dictionary-based matching of acquired signal evolution profiles to simultaneously generate quantitative maps of T_1 and T_2 relaxation times and proton density. This preclinical MRF acquisition was constructed from a Fast Imaging with Steady-state Free Precession (FISP) MRI pulse sequence to acquire 600 MRF images with both evolving T_1 and T_2 weighting in approximately 30 minutes. This initial high field preclinical MRF investigation demonstrated reproducible and differentiated estimates of *in vitro* phantoms with different relaxation times. *In vivo* preclinical MRF results in mouse kidneys and brain tumor models demonstrated an inherent resistance to respiratory motion artifacts as well as sensitivity to known pathology. These results

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suggest that MRF methodology may offer the opportunity for quantification of numerous MRI parameters for a wide variety of preclinical imaging applications.

Keywords

magnetic resonance fingerprinting; high field MRI; preclinical; mouse; kidney; brain; respiratory motion artifacts

INTRODUCTION

Over the past three decades, Magnetic Resonance Imaging (MRI) has become an established medical imaging modality due to its superior soft tissue contrast and lack of ionizing radiation. Conventional diagnostic MRI scans are non-quantitative by nature, but have provided clinicians and radiologists with the ability to detect multiple disease pathologies including cancer (1,2), stroke (3,4), musculoskeletal defects (5,6), and cardiovascular disease (7,8), among many others (9). Recently, efforts have been made to establish quantitative MRI assessments as biomarkers for disease detection and progression. These quantitative MRI assessments have included T_1 and T_2 relaxation times (10-12), proton density (11,12), multiple diffusion and perfusion parameters (13-18), as well as chemical exchange and magnetization transfer (19-24). Despite these efforts, the majority of routine clinical MRI scanning remains qualitative.

High field (4.7 T) preclinical MRI scanners have been developed to provide MRI measures of disease in rodent models. In contrast to clinical MRI scanning, preclinical MRI research studies are almost entirely quantitative by nature and may require assessment of multiple imaging parameters during a single scanning session. These quantitative preclinical MRI studies provide the opportunity to assess pathophysiologic changes associated with disease progression and therapeutic efficacy. In addition, rigorous validation of these preclinical MRI assessments has the potential to inform future clinical imaging studies. Therefore, a significant effort is ongoing to develop robust and effective preclinical MRI acquisition and reconstruction techniques.

Conventional MRI quantification methods are mostly based on linear or nonlinear curve fitting to various MRI models (11,25). The implementation of these established model-based methods, such as T_1 and T_2 relaxation time estimation, are straightforward. However, these conventional quantification methods are susceptible to multiple sources of errors including cardiac and respiratory motion artifacts (26-28), as well as inhomogeneity in the main magnetic field (B_0) (29). Importantly, the potential for these errors are significantly increased on high field preclinical MRI scanners where B_0 inhomogeneities are increased; rodent heart rates can be as high as 500-600 beats / minute; and breathholds are not possible. In addition, temporal errors can be observed in preclinical studies that require multiple imaging parameter estimates (ex. diffusion and perfusion) as extended periods of anesthesia can cause physiologic changes during sequential scans. Therefore, new MRI acquisition and reconstruction methods for preclinical imaging applications are needed that are immune to these error sources and can simultaneously obtain estimates of multiple imaging parameters.

Over the last few years, a new category of quantification in MRI has emerged which uses dictionary-based methods to “match” acquired data rather than conventional parameter estimation techniques using error-minimization methods. One of these methods, compressed sensing, has been developed for both clinical and preclinical applications and has been shown to limit quantification errors and/or reduce the overall time to acquire quantitative data sets (30-33). More recently, a new Magnetic Resonance Fingerprinting (MRF) methodology has been proposed (34). MRF uses an entirely unique acquisition and quantification strategy that combines *a priori* acquisition parameter variation with a dictionary-based matching algorithm to obtain quantitative assessments of multiple imaging parameters simultaneously. The MRF technique was initially developed for low-field (1.5T – 3T), clinical MRI scanners and was used to simultaneously generate T_1 , T_2 , and M_0 maps in healthy human brains. Further, this initial report determined that the MRF technique is inherently resistant to errors from motion artifacts as motion or noise is not included / encoded into the theoretical signal evolution profiles that make up the MRF dictionary (34). Therefore, MRF may provide an ideal basis to generate multi-parametric assessments for preclinical imaging applications with limited impact of motion artifacts.

In this study, we have developed an effective MRF acquisition and analysis algorithm for high field, preclinical MRI scanners. This is an initial implementation of the MRF technique on small animal MRI systems. For this initial implementation, we combined *a priori* variation in flip angles (FA) and repetition time (TR) with a Fast Imaging with Steady-state free Precession (FISP) acquisition (35,36) to simultaneously generate quantitative maps of T_1 and T_2 relaxation times and proton density (M_0) from a single scan. We have evaluated these MRF estimates of T_1 , T_2 , and M_0 in phantoms in comparison with conventional MRI techniques. We have obtained initial *in vivo* MRF data from healthy mouse kidneys to verify the robustness of the MRF technique to respiratory motion artifacts. We have also obtained *in vivo* MRF data from an orthotopic mouse glioma model to demonstrate the sensitivity of the MRF technique to known pathology. The impact of RF excitation pulse profile as well as the number of acquired MRF images on the T_1 , T_2 , and M_0 estimates have also been explored in this initial study.

METHODS

All animal studies were conducted in accordance with approved IACUC (Institutional Animal Care and Use Committee) protocols at Case Western Reserve University.

Preclinical MRF Acquisition and Reconstruction Design

The MRF acquisition was implemented on a Bruker Biospec 7 T MRI scanner (Billerica, MA) equipped with a 400 mT/m magnetic field gradient insert. The preclinical MRF acquisition was developed from a FISP acquisition to provide *a priori* variation in both flip angle (FA) and repetition time (TR) to generate T_1 and T_2 specific MRF signal evolution profiles as described previously for clinical MRF studies (34,36). A schematic of the MRF pulse sequence is shown in Fig. 1A. The MRF acquisition was initiated with an inversion preparation to enhance the overall T_1 sensitivity. The inversion preparation was followed by 600 successive FISP acquisition periods with varying excitation flip angle (FA, in degrees)

and repetition time (TR, in ms) variation (36). FA and TR variation profiles are shown in Fig. 1B and 1C, respectively. The echo time was held constant ($TE = 3.2$ ms) in this MRF implementation. A repeating sinusoidal FA pattern ranging from 0 to 70 degrees was implemented (Figure 1B). More FA lobes was used compared to original clinical MRF to provide additional image contrast. The TR pattern selected was a Perlin noise pattern (Figure 1C) similar to the original clinical MRF description. However, a higher range of TR values was used for this study (i.e., 12.0 ms to 25.3 ms) to obtain a reasonable signal-to-noise ratio (SNR) for the 600 MRF images (34).

To acquire the MRF signal evolutions, the MRF acquisition was designed to acquire the same line of k-space for each of 600 sequential images during each MRF-scan repetition period (11.6 seconds). The FISP-MRF kernel was designed with a filtered 7-lobe sinc radiofrequency (RF) excitation pulse ($\tau_{RF} = 2$ ms, bandwidth = 7000 Hz) to ensure a uniform excitation slice profile with limited excitation sidebands. Although not required, a 5-second delay was inserted after each MRF scan repetition (600 MRF-FISP TRs) to allow the magnetization to return to equilibrium prior to the next MRF scan repetition and to limit the duty cycle on the magnetic field gradients. This process was repeated for each line of k-space to generate 600 total temporal MRF images.

The MRF reconstruction process was implemented in Matlab (The Mathworks, Natick, MA). A fundamental component of the MRF reconstruction is the development of a large dictionary of signal evolution profiles that are subsequently “matched” to the acquired MRF signal evolution profile for each imaging voxel using vector-based inner product comparisons. The MRF dictionary was created as described previously using Bloch equation simulations of the MRF acquisition (34). The MRF dictionary consisted of 19,634 profiles generated from 199 T_1 values (100 to 2000 ms, increment = 10 ms; 2000 to 6000 ms, increment = 500 ms) and 101 T_2 values (10 to 150 ms, increment = 2 ms; 150 to 300 ms, increment = 5 ms). Unrealistic profiles with $T_1 < T_2$ were excluded. Note that the T_1 and T_2 increments in the MRF dictionary (2 – 10ms for low T_1/T_2 values) are small relative to the expected variation observed for *in vivo* T_1/T_2 estimates.

***In Vitro* MRF Assessments of T_1 and T_2 Relaxation Times and Proton Density (M_0)**

Four imaging phantoms with distinctly different T_1 and T_2 relaxation times were prepared by adding different concentrations of $MnCl_2$ (30, 100, 200, 300 μM , respectively) to distilled water. The solutions were added to 200 μL centrifuge tubes for imaging. Axial MRF images (600 total MRF images) were obtained for these phantoms. Additional MRF acquisition parameters for the phantom experiments were: FOV = 3 cm $\times$ 3 cm, matrix = 128 $\times$ 128, slice thickness = 1.5 mm, total acquisition time = 35 min 24 s. Although larger than typical, a slice thickness of 1.5mm was used for this initial preclinical MRF development to limit the effects of noise. Conventional inversion-recovery spin echo (IR-SE) (inversion delay times = [50, 200, 350, 500, 650, 800, 1000, 1500, 2000, 2500, 3000, 4000, 5000, 8000, 10,000] ms, TR/TE = 10,000 ms/8.1 ms, one average, total acquisition time = 6.7 h) and spin echo (SE) (echo times = [10, 25, 40, 60, 90, 120, 150, 300, 400, 500, 800] ms, TR = 10,000 ms, one average, total acquisition time = 3.9 h) methods were also implemented to generate conventional estimates of the phantom T_1 , T_2 , and M_0 values, respectively for comparison

with the MRF findings. All other imaging parameters including field of view and resolution were identical for the MRF, IR-SE (T_1), and SE (T_2 , M_0) acquisitions. Quantitative T_1 and T_2 relaxation times and proton density (M_0) maps were obtained from the MRF data. T_1 and T_2 relaxation time and M_0 maps were calculated for the conventional IR-SE and SE acquisitions using established methods (37).

The MRF and conventional acquisitions were repeated five times on different days to assess the reproducibility of the MRF estimates. Mean T_1 , T_2 , and M_0 values for all methods were obtained for each phantom using a region of interest (ROI) analysis. In addition, voxel-wise error maps and standard deviations for T_1 , T_2 , and M_0 were calculated to assess voxel-wise variation. Two-tailed Student's t-tests were used to compare the mean and voxel-wise variation in the MRF T_1 , T_2 , and M_0 values with the IR-SE and SE data, respectively.

Initial *In Vivo* and *Ex Vivo* Kidney MRF Assessments in a Healthy Mouse

In vivo and *ex vivo* MRF images were acquired for the kidneys of a 12-month old healthy mouse (C57/BL6, Jackson Labs) to assess the impact of respiratory motion. The mouse was initially anesthetized in 1-2% isoflurane with supplemental oxygen and positioned in a mouse volume coil for imaging (inner diameter = 35 mm). The body temperature and breathing rate of the animal were maintained at 35 ± 1 °C and 40 - 60 breaths/min with adjustable warm air and isoflurane levels, respectively. Single-slice, axial kidney MRF images were obtained for the mouse (FOV = 3 cm $\times$ 3 cm, matrix = 128 $\times$ 128, slice thickness = 1.5 mm). Importantly, no respiratory triggering was applied for these MRF acquisitions to demonstrate the robustness of the MRF technique to respiratory motion artifacts. Immediately following the *in vivo* MRF scans, the isoflurane concentration was increased to 5% for 30 minutes to euthanize the mouse within the MRI scanner with no repositioning. The MRF acquisition was then repeated on the same axial kidney imaging slice to generate an *ex vivo* MRF dataset with no respiratory motion artifacts. All MRF acquisition and reconstruction parameters for the *in vivo* and *ex vivo* kidney experiments were the same.

Initial MRF Assessments in a Mouse Brain Tumor Model

In vivo and *ex vivo* MRF assessments were also performed on mouse brains orthotopically implanted with a human glioma cell line expressing green fluorescent protein (GFP) to demonstrate the sensitivity of the MRF technique to known pathology and to examine the effects of RF excitation slice profile on the MRF estimates of T_1 , T_2 , and M_0 . To prepare the mouse glioma model, Gli36 cells were infected with GFP encoding lentivirus, harvested for intracranial implantation by trypsinization, and concentrated to 1×10^5 cells/ μ L in PBS as described previously (38). A six-week old female athymic nude mouse was anesthetized by intraperitoneal administration of 50 mg/kg ketamine/xylazine and fitted into a stereotaxic rodent frame (David Kopf Instruments, Tujunga, CA). Tumor cells were implanted at AP = +0.5 and ML = -2.0 from the bregma in the right striatum at a depth of 3 mm below the dura using a 10- μ L syringe (26-gauge needle; Hamilton Co, Reno, NV). A total of 200,000 glioma cells were implanted.

In vivo MRF scans were obtained 8 days following inoculation with the tumor cells. As for the kidney MRF studies, the animal was anesthetized with 1-2% isoflurane and positioned within a 35-mm inner diameter volume coil within the 7 T Bruker Biospec MRI scanner. Conventional T₂-weighted images of the glioma model were obtained from a Rapid Acquisition with Relaxation Enhancement (RARE) acquisition (TR/TE = 3000 ms / 40.0 ms, FOV = 3 × 3 cm, matrix = 256 × 256, slice thickness = 1.5 mm, three averages, total acquisition time = 8 min) to identify the tumor region (39). The MRF parameters for the *in vivo* brain tumor assessments were (FOV = 3 cm × 3 cm, matrix = 128 × 128, slice thickness = 1.5 mm, excitation sinc7 pulse, total acquisition time = 35 min 24 s). The *in vivo* brain MRF data were used to generate T₁, T₂, and M₀ maps reconstructed from the full MRF dataset (600 images) as well as subsets of 100, 300, and 500, images respectively to determine the number of MRF images needed for effective quantification. Mean brain T₁, T₂, and M₀ values were obtained from an ROI analysis of each set of MRF reconstructions for comparison.

Ex vivo MRF scans of a separate excised mouse brain tumor model were acquired to obtain an initial investigation into the impact of excitation slice profile on MRF estimates. The mouse glioma model was prepared as described above. After 10 days of tumor growth, the animal was sacrificed, and the brain was excised for fluorescence imaging using a Maestro FLEX fluorescence scanner (CRi, Hopkinton, MA) to verify tumor viability. Fluorescence images of the GFP-expressing Gli36-5 tumor cells were acquired using standard GFP filters (excitation = 445-490 nm, emission = 515 nm long-pass filter, acquisition settings = 500-720 in 10-nm steps). Brightfield images were also acquired to provide an anatomic roadmap. Fluorescence and brightfield exposure durations were 10 milliseconds and 300 milliseconds, respectively. Fluorescence images were background subtracted and unmixed, using the Maestro software to spectrally separate brain auto-fluorescence from GFP-expressing tumor cells. The brain was then placed in neutral buffered 10% formalin (Sigma-Aldrich, Milwaukee, WI, USA) within a 15mL centrifuge tube for *ex vivo* MRF imaging.

The MRF acquisition (FOV = 3 cm × 3 cm, matrix = 128 × 128, slice thickness = 1.5 mm, total acquisition time = 35 min 24 s) was repeated using either a filtered 7-lobe sinc radiofrequency (RF) excitation pulse (τ_{RF} = 2 ms) or a hermite RF excitation pulse (τ_{RF} = 2 ms). The slice profiles for each RF excitation pulse were measured using a conventional Fast Low Angle SHot (FLASH) acquisition (FOV = 1.52 cm × 1.52 cm, matrix = 256 × 256, TR/TE = 100.0 ms/10.0 ms, FA = 10 degrees) by applying the readout gradient along the axial slice-select direction as described previously (40). Although the sinc7 pulse would be expected to provide a more uniform excitation with reduced sidebands, these two pulses were selected as they are commonly used for many preclinical MRI acquisitions. Following the *ex vivo* MRF acquisition, the mouse brain was sectioned at 8 μ m per section and stained with hematoxylin and eosin (H&E) stains to further validate the existence of the brain tumor.

RESULTS

Example *in vitro* phantom images of MnCl₂-doped phantoms at multiple MRF timepoints (image numbers 40, 80, and 150 out of 600 total) and single-voxel signal evolution profiles

are shown in Figures 2A and 2B, respectively. The three selected time points (image 40, 80, 150) are indicated with arrows in Figure 2B. Note the varying contrast in the phantom images at the three selected time points. Note the reasonable match between the acquired (in red) and matched dictionary (in blue) MRF signal evolution profiles for all four phantoms.

Resultant MRF-based T_1 (Fig. 3A), T_2 (Fig. 3B), and M_0 maps (Fig. 3C) for the four $MnCl_2$ -doped water phantoms are shown in Figure 3. Corresponding T_1 , T_2 , M_0 maps from the conventional IR-SE (T_1 , Fig. 3D) and SE (T_2 , Fig. 3E, M_0 , Fig. 3F) are shown for comparison. Differential error maps (MRF estimate – conventional estimate) for T_1 , T_2 , and M_0 are shown in Figures 3G, 3H, and 3I, respectively.

Quantitative evaluation of these *in vitro* MRF and conventional maps are shown in Figure 4. Mean ($\pm$ standard deviations) T_1 , T_2 and M_0 values for the MRF and conventional methods from an ROI analysis of the five repeat scans are shown in Figure 4A. The MRF-based T_1 estimates for all four phantoms were not statistically different from the conventional IR-SE T_1 maps ($p > 0.1$), while the mean T_2 and M_0 MRF estimates exhibited some significant differences. The mean T_2 estimates from the MRF scans were significantly higher than from the conventional SE methods for three of the four phantoms ($p < 0.01$) while the phantom with the highest T_2 value was significantly lower than the estimates from the conventional SE methods ($p < 0.01$). Two of the four phantoms had significant higher M_0 values from MRF scans compared to SE methods ($p < 0.05$). Despite these differences, the MRF results showed significant decreases in both T_1 and T_2 values for increasing $MnCl_2$ concentrations as expected ($p < 0.01$) (41).

A comparison of the mean ($\pm$ standard deviations) voxel-wise variation in the T_1 , T_2 and M_0 maps from the MRF and conventional acquisitions are shown in Figure 4B. The voxel-wise variation in the MRF-based T_1 estimates was significantly lower than for the conventional IR-SE method for 2 of 4 phantoms suggestive of improved uniformity of the MRF T_1 maps ($p < 0.05$). The voxel-wise variation in the MRF T_1 estimates was less than 20 ms for all four phantoms. The voxel-wise variation in the MRF T_2 maps was less than 10 ms for all four phantoms, but the variation was significantly increased relative to conventional methods for three of the four phantoms ($p < 0.05$). No significant differences were observed in the voxel-wise variation in the proton density maps and all mean variation values were less than 0.08.

Axial MRF T_1 , T_2 , and M_0 maps of the same kidneys of a healthy mouse both before (Fig. 5A, *in vivo*) and after euthanasia (Fig. 5B, *ex vivo*) are shown in Figure 5. Importantly, the *in vivo* kidney T_1 , T_2 , and M_0 maps are devoid of respiratory motion artifacts typical of conventional *in vivo* preclinical scans. Hyperintense regions in the T_1 and T_2 maps were also observed in the renal medulla as expected (42). The *in vivo* MRF T_2 maps showed increased ghosting artifacts near the abdominal aorta possibly due to aortic pulsatility. Otherwise, the *in vivo* and *ex vivo* kidney maps are very similar with only regional decreases in the *ex vivo* T_1 , T_2 , and M_0 values likely due to the absence of flowing blood. As further verification, MRF signal profiles and respective “matched” dictionary profiles are shown in Figure 5C and 5D from an ROI of the right *in vivo* and *ex vivo* renal cortex (ROI shown in blue in T_1 maps). Note the similar shape of the acquired MRF profiles aside from the respiratory

motion “spikes” for the *in vivo* MRF scan (arrows in Fig. 5C). Importantly, the matched MRF profile (in blue) for the *in vivo* scan appeared to ignore these respiration spikes as the motion is not encoded in the theoretical signal evolution profiles in the MRF dictionary.

In vivo MRF-based T_1 , T_2 , and M_0 maps of a mouse brain orthotopically implanted with a human glioma cell line are shown in Figures 6A, 6B and 6C, respectively. Corresponding T_2 -weighted anatomic MRI images, combined fluorescence and brightfield images of the GFP expressing glioma cells, and H&E stain validating tumor presence and location (arrows in Figure 6F) are shown in Figure 6D, 6E, and 6F, respectively. An ROI analysis showed mean T_1 , T_2 and M_0 values in the glioma ($T_1 = 1973$ ms, $T_2 = 82$ ms, $M_0 = 0.5$ ms), cerebral cortex ($T_1 = 1470$ ms, $T_2 = 63$ ms, $M_0 = 0.4$) and thalamus ($T_1 = 1273$ ms, $T_2 = 55$ ms, $M_0 = 0.4$ ms) that are comparable to results in previous studies (43-45). No ghosting artifacts were observed in these *in vivo* MRF T_2 maps of a mouse brain.

The T_1 , T_2 , and M_0 maps were reconstructed from subsets of the same *in vivo* MRF data using the first 100, 300, 500, and 600 images in the MRF profile, respectively (Figure 7). The MRF maps obtained from reconstruction of the full dataset ($N=600$, same as Figure 6)) are included as a reference. Mean brain T_1 , T_2 , M_0 values using the first 600, 500, and 300 images were consistent (range of mean $T_1 = 1436$ to 1461 ms; range of mean $T_2 = 65$ - 69 ms; range of mean $M_0 = 0.4$ - 0.5). However, the mean values were substantially different using only the first 100 MRF images in the matching process ($T_1 = 1648$ ms, $T_2 = 52$ ms, $M_0 = 0.8$). While not a rigorous evaluation, these initial findings suggest the importance of acquiring a sufficient number of MRF images as well as opportunities for optimizations to reduce the overall MRF acquisition time.

MRF T_1 , T_2 , and M_0 maps were also generated from an *ex vivo* mouse brain with an implanted glioma using either a sinc7 (Fig. 8A) or hermite (Fig. 8B) RF excitation pulses in the MRF-FISP acquisition. The magnitude of the RF excitation pulse shape and the corresponding measured slice profiles obtained from the conventional FLASH acquisition are shown for both excitation pulses. Note that the sinc7 excitation pulse provides a more uniform tip angle across the entire imaging slice (vertical dashed lines) and reduced side-band excitations in comparison to the hermite excitation pulse, as expected. The MRF T_1 and T_2 estimates using the sinc7 RF pulse ($T_1 = 970$ ms, $T_2 = 59$ ms, $M_0 = 0.8$) were lower relative to the corresponding values obtained with the hermite pulse ($T_1 = 1078$ ms, $T_2 = 146$ ms, $M_0 = 0.7$), while the M_0 values were slightly lower. Overall, the T_2 estimates appear to be more sensitive to excitation profile as the estimates obtained from the sinc7 pulse ($T_2 = 59$ ms) were approximately one half that obtained from the hermite pulse ($T_2 = 146$ ms).

DISCUSSION

We have developed an initial implementation of the novel Magnetic Resonance Fingerprinting (MRF) technique specifically for high field preclinical MRI scanners. This preclinical MRF implementation builds upon the previously-reported clinical MRF implementation and combines *a priori* flip angle and repetition time variation profiles with an inversion preparation and a FISP imaging acquisition kernel to obtain MRF signal

evolution profiles that are sensitive to T_1 and T_2 relaxation times as well as proton density (34,36,46). Herein, we have shown that the MRF methodology can provide quantitative *in vivo* assessments of T_1 , T_2 , and M_0 of mouse brain and kidneys with no respiratory motion artifacts. In addition, the simultaneous estimation of multiple imaging parameters provides the opportunity to identify and quantify tissue pathophysiology without the physiologic confounds of conventional methods that require sequential parameter estimation (47). As such, this MRF technique provides a uniquely powerful imaging platform that can be used to assess disease pathophysiology and therapeutic efficacy in a wide variety of rodent disease models.

An important design criteria for the MRF acquisition is the use of a FISP imaging kernel instead of True FISP or EPI imaging kernels to limit “banding” and distortion / ghosting artifacts, respectively in the dynamic MRF images. Importantly, these artifacts are especially problematic on high field MRI scanners due to increased B_0 inhomogeneities (36,48,49). The FISP acquisition also provides increased T_2 sensitivity in comparison with other incoherent steady-state MRI techniques such as FLASH acquisitions (35). The MRF-FISP FA and TR variation profiles (Fig. 1B and 1C) were modified slightly for this implementation to increase the sensitivity of the signal evolution profiles to the relaxation parameters. For example, the sinusoidal FA profiles were expanded to provide sufficient T_1 and T_2 weighting over the 600 MRF images (Fig. 2A). In addition, the Perlin-noise TR variation profile used in the original clinical MRF study was used in this initial implementation, albeit with an expanded TR range to increase the SNR of the MRF images. The preclinical MRF dictionary was also adjusted to reflect the increased T_1 and decreased T_2 values observed on high field MRI scanners.

The *in vitro* MRF results shown in Figures 2-4 demonstrate that the MRF methodology is at least comparable to conventional quantitative assessments. The *in vitro* T_1 and M_0 values are similar for both the MRF and conventional measures and resulted in significantly different mean T_1 values for the different $MnCl_2$ -doped phantoms as expected ($p < 0.0001$). Importantly, it appears that the MRF-based T_1 estimate is significantly more uniform than conventional measures (Fig. 4B). These results are consistent with the original clinical MRF report comparing MRF with DESPOT1 and DESPOT2. While the MRF-based T_2 estimates also differentiated the *in vitro* phantoms ($p < 0.01$), the MRF-estimates were also significantly different than the estimates from the conventional spin echo methods for all four phantoms. Interestingly, the MRF-based T_2 estimate were all lower than the conventional methods except for the phantom with the highest T_2 value. In addition, the MRF T_2 estimates resulted in increased voxel-wise variation (Fig. 4B). The differences in mean T_2 values and relative increases in non-uniformity may be due to multiple factors. While a thorough investigation of these mechanisms is beyond the scope of this initial publication, we would not expect the small increments in the T_1 (i.e., 10 ms) and T_2 (i.e., 2 ms) relaxation times used in the MRF dictionary to have a major impact on the quantification. However, two other factors are likely to be important: 1) unintended diffusion weighting in both the MRF-FISP acquisition as well as from the crusher gradients in the conventional spin echo acquisitions; and 2) heterogeneity / errors in the RF excitation field (B_1). It can be expected that diffusion weighting is inherently present in many MRI

acquisitions to varying degrees and may be accounted for in future MRF studies (50). In this initial work, we have already observed a significant impact of small B_1 heterogeneity errors specifically on the T_2 estimates as shown in Figure 8. In switching from sinc7 to hermite RF excitation pulses, The MRF T_2 estimates for the *in vitro* mouse brain increase from ~60ms (sinc7, Fig. 8A) to ~140ms (hermite, Fig. 8B). At the same time, the T_1 and M_0 values also change, but to a much smaller degree. Therefore, an important next step in preclinical MRF development will be to incorporate B_1 corrections into the MRF dictionary / reconstruction process in order to improve both the accuracy as well as the uniformity of the T_2 estimates. These imperfections in slice profile / tip angle, along with high noise levels, may result in imperfect matches between the acquired and theoretical signal evolution profiles. A straightforward method to correct for B_1 inhomogeneities is to measure the B_1 field directly (51,52) either before or after the MRF scans (46). While not implemented herein, this important limitation will need to be addressed in future studies to enable use of highly sensitive, but non-uniform, surface coils, which are used frequently in preclinical imaging applications (53).

As mentioned above and shown in the *in vivo* / *ex vivo* mouse kidney images in Figure 5, a key advantage of the MRF technique is its inherent resistance to bulk motion artifacts. This resistance to motion artifacts is consistent with the previous clinical MRF report which generated robust axial brain maps despite conspicuous rotational head motion (34). This is an essential feature for all *in vivo* preclinical imaging applications because of the lack of breathholding and provides the opportunity to avoid respiratory motion artifacts and/or respiratory gating for rodent imaging applications. The underlying cause of the inherent motion insensitivity of the MRF technique lies in the fact that respiration rates in mice under isoflurane anesthesia are typically 40-60 breaths / minute and no respiratory motion is observed for a majority of the time between breaths. This ~1 second quiescent period allows up to 100 motion-free MRF data points to be acquired in between the ~100 ms respiration “spikes” as shown in Figure 5C. At the same time, the respiratory motion “spikes” were not included in the theoretical MRF dictionary profiles. Therefore, the spikes were ignored in the MRF matching process to generate parameter estimates for each voxel with minimal impact of respiratory motion. It is worth noting that significant ghosting artifacts were observed near the abdominal aorta of the *in vivo* kidney T_2 maps (Fig. 5A). As these ghosting artifacts are also absent in the *ex vivo* maps, it seems likely that these artifacts are due to aortic pulsatility. Interestingly, these ghosting artifacts were not observed in the mouse brain T_2 maps possibly due to reduced flow rate and / or vascular motion. While the specific cause of these ghosting artifacts was not explored in this initial preclinical MRF development, these mouse brain results suggest that the MRF methodology can be designed to limit a range of motion and / or flow artifacts.

Importantly, the preclinical MRF technique, as described herein, can be significantly expanded and/or improved in future studies. As for the clinical MRF study, non-Cartesian trajectories (e.g. radial, spiral) can be incorporated to reduce the overall acquisition time to acquire the MRF image sets. For example, utilization of a single-shot spiral trajectory, as shown in the original MRF methodology, could potentially reduce the overall acquisition time to as little as 10-20 seconds for each imaging slice (34). Parallel imaging and/or

compressed sensing strategies could also be incorporated to enable reductions in both Cartesian and non-Cartesian MRF trajectories. Further, the results shown in Figure 7 suggest that the number of MRF images could be immediately halved to 300 images with limited impact on T_1 and T_2 quantification. These reductions in MRF acquisition time could then be utilized to develop effective multi-slice 2D or 3D MRF acquisitions. A rapid 3D MRF acquisition, in particular, would help to acquire high resolution MRF images (slice thickness < 1.5 mm as used herein) with sufficient SNR to reliably generate quantitative MRF assessments.

Another important area for expansion of this preclinical MRF technique is to explore quantification of other important MRI parameters. While this initial implementation focused primarily on estimation of T_1 and T_2 relaxation times and proton density, the MRF-FISP acquisition could be modified to simultaneously estimate perfusion and diffusion parameters which are important in non-invasively assessing ischemic diseases such as stroke (13), acute kidney injury [AKI (54)], and cardiac injury models (55). A recent publication on MR vascular fingerprinting describes the potential application of MRF in human neural perfusion quantification (56). Fundamentally, there are only two components required to adapt the MRF techniques to these other parameters. First, the MRF acquisition must be designed to dynamically generate MRF images with variable contrast weighting due to the parameters to be estimated. The second component is to design the MRF dictionary based on the Bloch equations and the specific MRF acquisition. However, the process of designing an ideal MRF acquisition and dictionary remains somewhat empirical. Further, the impact of specific components of the MRF-FISP acquisition including the timing and frequency of the inversion preparation and / or other preparation schemes on the signal evolution profiles and parameter estimates is an open area for study.

In conclusion, we have developed a Magnetic Resonance Fingerprinting (MRF) technique specifically for high field small animal MRI scanners. We have implemented an MRF-FISP acquisition which minimizes artifacts on high field scanners with an inversion preparation to generate both T_1 and T_2 sensitivity in the dynamic MRF acquisition. In combination with the MRF dictionary, the MRF-FISP acquisition resulted in simultaneous T_1 , T_2 , and proton density maps of both phantoms and mouse brain and kidneys in a single acquisition. Most importantly, the MRF methodology has demonstrated inherent resistance to respiratory motion artifacts in mouse kidney imaging applications. This is a significant improvement over conventional MRI techniques relying on either breathholding or respiratory gating which are either not possible or frequently unreliable in preclinical imaging applications. Initial *in vivo* mouse brain tumor studies also demonstrate sensitivity to known pathology. This MRF technique can also be adapted to assess other MRI parameters including diffusion and perfusion establishing a platform of MRI technology to enable multi-parametric imaging assessments in rodent models to assess mechanisms of disease initiation and progression as well as the efficacy of novel therapies.

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Abbreviations used

MRF	magnetic resonance fingerprinting
FISP	fast imaging with steady-state free precession
SNR	signal-to-noise ratio
IR-SE	inversion-recovery spin echo
ROI	region of interest
GFP	green fluorescent protein
RARE	rapid acquisition with Relaxation Enhancement
FLASH	fast low angle shot
AKI	acute kidney injury
H&E	hematoxylin and eosin

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Figure 1.

(A) Schematic of the MRF-FISP pulse sequence with one line of k-space acquired for each of N images in one MRF scan repetition ($N=600$ for this initial implementation). (B,C) Flip angle and repetition time variation profiles used to create the MRF acquisition and dictionary.

Figure 2.

(A) *In vitro* MRF images from four MnCl_2 -doped phantoms with varying T_1 and T_2 relaxation times. Images acquired at multiple timepoints (image 40, 80, and 150) show evolving contrast during the dynamic MRF acquisition. (B) Signal evolution profiles from the four phantoms with acquired data profile (in red) and corresponding “matched” dictionary profile (in blue). Arrows delineate the specific timepoints for the three phantom images.

Figure 3.

(A,B,C) Quantitative axial phantom MRF maps of T_1 , T_2 , and M_0 . (D,E,F) T_1 , T_2 relaxation times and M_0 maps from conventional inversion recovery spin echo (IR-SE) and spin echo (SE) acquisitions, respectively for comparison. (G,H,I) Error maps of T_1 , T_2 and M_0 (MRF estimate – conventional estimate).

Figure 4.

(A) Plots of mean phantom T_1 , T_2 and M_0 values from MRF and conventional methods over five scans on different days. Error bars represent one standard deviation in the mean value across all five measurements. (B) Plots of mean voxel-wise standard deviation for T_1 , T_2 and M_0 values from MRF and conventional methods as a measure of intrascan uniformity. Error bars represent one standard deviation in the mean value across all five measurements.

Figure 5. MRF T_1 , T_2 , M_0 maps from (A) *in vivo* healthy mouse kidneys and (B) the same imaging slice after euthanasia. (C) Acquired (in red) and matched (in blue) MRF signal evolution profiles of mouse kidney cortex from *in vivo* and (D) *ex vivo* scans. Note the overall similarity of the matched MRF profiles and resistance to respiratory motion spikes (arrows) visible in the acquired *in vivo* MRF profile, but not visible in the *ex vivo* MRF profile.

Figure 6.
(A,B,C) *In vivo* MRF T_1 , T_2 and M_0 maps of a mouse brain with a GFP-expressing Gli36-5 tumor. (D) T_2 -weighted image as an anatomic and tumor contrast reference. (E) Coronal brightfield image (gray scale) with GFP overlay and (F) H&E image confirming tumor location (arrows).

Figure 7.

MRF T_1 (top row), T_2 (middle row) relaxation time and M_0 (bottom row) maps of the *in vivo* mouse brain with implanted tumor shown as a function of the number of acquired and matched MRF images. Note that the T_1 and T_2 maps are consistent with 300 MRF-FISP images suggesting opportunities for significant reduction in the MRF acquisition time.

Figure 8.

Ex vivo MRF T_1 , T_2 and M_0 maps of an excised mouse brain and glioma using either (A) sinc7 or (B) hermite radiofrequency (RF) excitation pulses for the MRF-FISP acquisition. The RF waveforms and measured slice profiles are also included. Note the sensitivity of the MRF technique, in particular the T_2 estimates, to slice profile errors.