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Magnetization recovery for signal enhancement: a fast imaging DEFT-based technique

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Abstract

This paper describes the development and application of a new fast MRI technique based on the DEFT principle. The sequence named MAgnetization RecoverY for Signal Enhancement (MARYSE) is composed of two completely symmetric gradient echoes separated by a 180° refocusing pulse. The RF pulse scheme, $90°_x$–$180°_y$–$90°_{-x}$ enables restoration of the transverse magnetization along the longitudinal axis, and consequently artificially increases R_1 relaxation rate. In this sequence, the period between the excitation pulse and the restoring pulse (Tem: transverse magnetization evolution time) is very short (<10 ms). This makes possible a significant increase in signal-to-noise ratio, even with a relatively short repetition time (20 ms). Simulations were performed for different values of Tem and TR at definite T_1 and T_2 and for different values of T_1 and T_2 at constant Tem and TR. Relevant signal enhancement for species with long relaxation time constants as compared to classical gradient echo and fast spin-echo imaging was expected. In vitro studies on a fat/water phantom confirmed this simulation. Application of MARYSE to mouse brain imaging permitted to visualize almost completely cerebrospinal fluid of the ventricles, a signal usually partially saturated in fast gradient echo imaging.

Keywords: MRI; Fast imaging; High resolution; Gradient echo; DEFT

1. Introduction

Recent research in genomics and hope of gene therapy raised the need for non-invasive investigation of normal or transgenic small animals. Among the biological imaging techniques, Magnetic Resonance Imaging, with the diversity of generated contrast and high potential spatial resolution constitutes an excellent tool. Well-resolved images with pixel size smaller than 200 μm are necessary, particularly in mouse models, to visualize anatomic details like early tumors, heart or vessels [1,2]. Unfortunately, this increase in spatial resolution is often associated with a loss of sensitivity.

To compensate this, several solutions have been investigated. The design of coils with high quality factor, like surface microcoils [3] or superconducting probes [4] allowed investigation of very small structures. The complementary and more popular approach is the use of ultrahigh static magnetic fields and gradient strengths. Recent developments in NMR microscopy made it possible to obtain very well-resolved images (<5 μm) in plants or phantoms [5]. In biological living systems, larger voxel sizes are commonly achieved. Lower resolutions are often due to necessarily shorter acquisition time and to poor magnetic field homogeneity. Moreover high magnetic field systems are associated with a number of difficulties, including the considerable susceptibility effects. They cause rapid dephasing of transverse magnetization resulting in a loss of signal. The use of spin-echo or gradient echo sequences with very short echo time could partly circumvent this problem. From this point of view, fast imaging techniques, like FLASH [6], are particularly interesting. They permit acquisition of 3D images that bear a high signal-to-noise ratio (SNR) and good spatial resolution in the three dimensions. They are particularly useful for vascular system investigation (Magnetic Resonance Angiography).

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Nevertheless, the use of very short repetition time has another drawback, particularly at high field: partial saturation of substances with long longitudinal relaxation times. This results in a significant reduction of signal, especially for liquids like blood or cerebrospinal fluid (CSF). Relaxation contrast agents like gadolinium could be an alternative [7] as well as imaging techniques with high SNR efficiency like True-Fisp [8].

Another interesting approach to improve SNR is the use of a sequence based on the driven equilibrium Fourier transform (DEFT) principle, first proposed by Becker et al. [9] in high resolution ^{13}C NMR. The goal of this method is to establish a higher steady state longitudinal magnetization for substances with high T_1 values and consequently to reduce recovery time. This scheme has been successfully applied in MRI to enhance resolution and/or signal-to-noise ratio [10,11]. More recently Hargreaves et al. [12] used DEFT to provide good contrast in joints because of enhanced signal from joint fluid due to their long T_1 and T_2. An alternative pulse sequence based on DEFT proposed by Ugurbil et al. [13] has also yielded T_1-weighted images of the human brain at very high magnetic field [14].

DEFT imaging has been achieved using a double spin-echo sequence, $90°_x$–TE/2–$180°_y$–TE/2–echo–TE/2–$180°_y$–TE/2–$90°_{-x}$ [11]. Data were acquired during the first echo and the transverse magnetization was restored along the z-axis during the second echo. However, some drawbacks limit the application of this sequence. As it is composed of two spin-echoes, both echo and repetition times are longer compared to a gradient echo. To our knowledge, in spite of its high SNR, DEFT has not been applied to fast imaging. The repetition time classically used for DEFT was greater than 200 ms and the time between the excitation pulse and the restoring pulse (Tem) was greater than 20 ms. Nevertheless, a significant increase in SNR could be obtained with very short Tem.

The aim of this study was to develop a DEFT sequence with minimum Tem. It is called MAgnetization RecoverY for Signal Enhancement (MARYSE) and could be applied for relatively fast imaging. Two completely symmetric gradient echoes separated by a 180° refocusing pulse were implemented. The results show a significant increase in SNR for long T_1 and T_2 values as compared to fast spin-echo (RARE) [15] and fast gradient echo imaging.

2. Materials and methods

2.1. Hardware

Experiments were carried out on a 4.7 T Bruker Biospec 47/50 (Bruker, Ettlingen, Germany). The system was equipped with a 6 cm BG6 gradient system capable of 950 mT/m maximum strength and 50 μs rise time. Measurements were performed with a birdcage resonator (35 mm diameter and 80 mm length) tuned at 200.3 MHz.

2.2. Phantom

Fat/water contrast was assessed on a phantom made of a 5 mm diameter vial filled with vegetable oil ($T_1 = 350 \pm 20$ ms; $T_2 = 45 \pm 2$ ms) inserted in 20 mm diameter tube containing water ($T_1 = 2450 \pm 120$ ms; $T_2 = 550 \pm 27$ ms). To ensure adequate B_1-field homogeneity, sensitivity enhancements were measured on a 5 mm diameter water tube positioned at the symmetry axis of the RF coil. Longitudinal relaxation time constants were measured with the inversion recovery technique and transverse relaxation times using the CPMG pulse sequence (32 echoes).

2.3. Animal preparation

Mice C57 black 6 (body weight 20–30 g) were anesthetized with Isoflurane (1% in air). Animals were positioned prone within the magnet, their head placed at the center of the NMR coil.

2.4. Simulations

Simulations were performed with Igor Pro (Wavemetrics, Lake Oswego, OR) data processing software.

2.5. NMR imaging

Phantom experiments. Single slice 2D images (Matrix size: 128×128; FOV: 40×40 mm; slice thickness: 5 mm; 32 scans) were recorded using three different protocols.

- MARYSE: flip angle: 90°; TR/TE/Tem = 20/1.7/7 ms (first echo) or TR/TE/Tem = 20/5.3/7 ms (second echo); total acquisition time: 1 min 22 s.
- Gradient echo: Ernst flip angle for water: 7°; TR/TE = 20/1.7 ms; total acquisition time, 1 min 22 s.
- Fast spin-echo: flip angle: 90°; TR/effective TE: 3718/69 ms; 16 echoes per TR; total acquisition time, 15 min 52 s.

Mouse brain experiments:

- MARYSE: 3D imaging; FOV: $21 \times 21 \times 25$ mm; Matrix: $192 \times 192 \times 32$; flip angle: 90°; TR/TE/Tem: 20/1.7/7 ms; 12 scans; total acquisition time: 24 min 35 s.
- gradient echo: 3D imaging; FOV: $21 \times 21 \times 25$ mm; Matrix: $192 \times 192 \times 32$; flip angle: 15°; TR/TE = 20/1.7 ms; 12 scans; total acquisition time: 24 min 35 s).
- fast spin-echo: 2D imaging; FOV: 21×21 mm; slice thickness: 1 mm; matrix: 192×192; 16 echoes per TR; TR = 3718 ms; effective TE = 69 ms; 18 slices; 64 scans; total acquisition time: 47 min 35 s.

2.6. 3D segmentation

3D reconstructions are performed with MRIcro free software written by Chris Rorden (Psychology Department, University of Nottingham).

3. MARYSE sequence

The pulse sequence proposed by Becker et al. [9] for high resolution NMR spectroscopy was $90°_{x}$–$180°_{y}$–$90°_{-x}$. Data were acquired during the free induction decay created by the first excitation pulse and during the first half of the echo generated by the refocusing pulse. MARYSE was based upon a similar pulse program, but the first decay was space-encoded with a classical gradient echo (echo 1 in Fig. 1). Due to the symmetry with respect to the central π-pulse, a second reverse gradient echo can be read (echo 2).

Some adjustments were necessary to ensure image quality. An adiabatic hyperbolic secant π pulse, with a large bandwidth (11,700 Hz) was used for on-resonance refocusing [16]. Phase and slice (for 3D) rewinder gradients were also implemented. They allowed minimization of phase errors introduced by a non-perfect 180° refocusing pulse. More generally, the first-order momentum of any gradient pulse was the same for each Tem/2 period. Moreover, the $180°_{y}$ refocusing pulse must be exactly centered at Tem/2 for a better efficiency of the $90°_{-x}$ longitudinal magnetization restoring pulse. On both sides of the π pulse, as little crusher gradients as possible were also implemented, a compromise to spoil unwanted coherence generated by imperfect refocusing and to limit the decrease in transverse magnetization. Finally, spoiling gradients may be necessary after the $90°_{-x}$ pulse to suppress transverse magnetization generated by its imperfection.

4. Theory

The signal generated by the MARYSE sequence is similar to the well-known DEFT signal described by Becker and co-worker [17]. Here, the excitation flip angle is 90°, and Tem is the period between the two 90° pulses. Under steady state, the NMR signal is a combination of T_2 relaxation during Tem and T_1 relaxation during TR-Tem (Eq. (1)).

$$M_{xy,\mathrm{MARYSE}} = M_0 \frac{1-\exp[-(\mathrm{TR}-\mathrm{Tem})/T_1]}{1-\exp(-\mathrm{TR}/T_1+\mathrm{Tem}/T_1-\mathrm{Tem}/T_2)} \times \exp-(\mathrm{TE}/T_2^*). \quad (1)$$

4.1. Signal-to-noise

The signal occurring from a gradient echo in MARYSE was compared to the signal of a classical gradient echo. Signal from gradient echo without restoring longitudinal magnetization is described with the partial saturation equation [18]. Optimal signal-to-noise ratio is obtained at the Ernst angle ($\cos\alpha_{\mathrm{opt}} = \exp(-\mathrm{TR}/T_1)$) (Eq. (2)).

$$M_{xy,\mathrm{GE\_ERNST}} = M_0 \sin\alpha_{\mathrm{opt}} \frac{1-\exp(-\mathrm{TR}/T_1)}{1-\exp^2(-\mathrm{TR}/T_1)} \times \exp-(\mathrm{TE}/T_2^*). \quad (2)$$

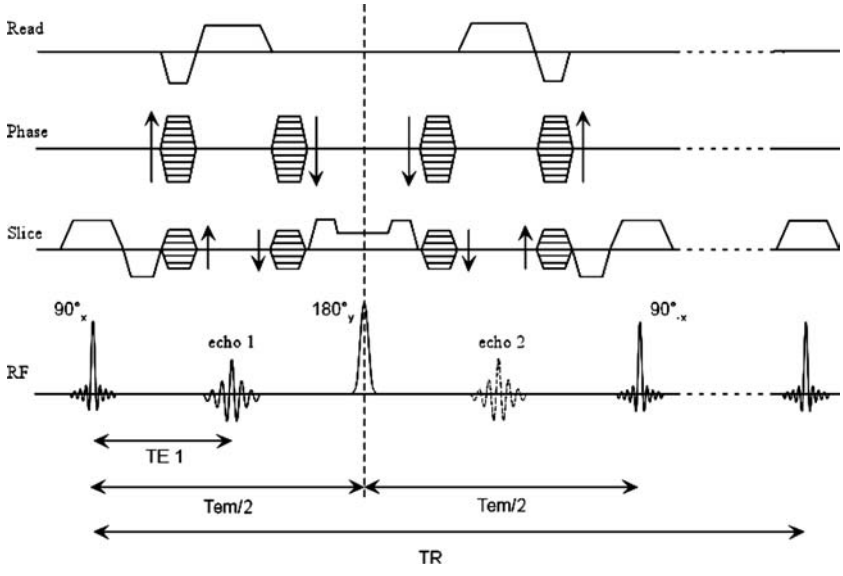

Fig. 1. Chronogram of the 3D MARYSE sequence. Excitation and restoring were achieved by sine pulses (800 μs), refocusing pulse was a hyperbolic secant pulse with a duration of 1500 μs and a bandwidth of 11,700 Hz. Two gradient echoes (echo 1 and 2) could be sampled within a single repetition time.

In Eq. (3) is defined the sensitivity ratio E for MARYSE compared to partial saturation obtained in a gradient echo using excitation at the Ernst angle. The transverse relaxation time T_2^* does not appear because its contribution is the same in Eqs. (1) and (2).

$$E = \frac{M_{xy,\mathrm{MARYSE}}}{M_{xy,\mathrm{GE\_ERNST}}}. \quad (3)$$

In simulations of the sensitivity enhancement E in the water phantom ($T_1 = 2450$ ms; $T_2 = 550$ ms), Tem varied from 0 to 20 ms and TR varied from 0 to 200 ms (Fig. 2). As seen in Fig. 2, Tem should be as small as possible to obtain a significant enhancement of signal-to-noise ratio. Recent gradient systems make possible echo time and repetition time lower than 1 and 3 ms, respectively. For Tem lower than 10 ms and a repetition time equal to 20 ms, the expected theoretical sensitivity enhancement is rather high (between 4.5 and 6.5). Under such conditions the MARYSE sequence is thus potentially useful.

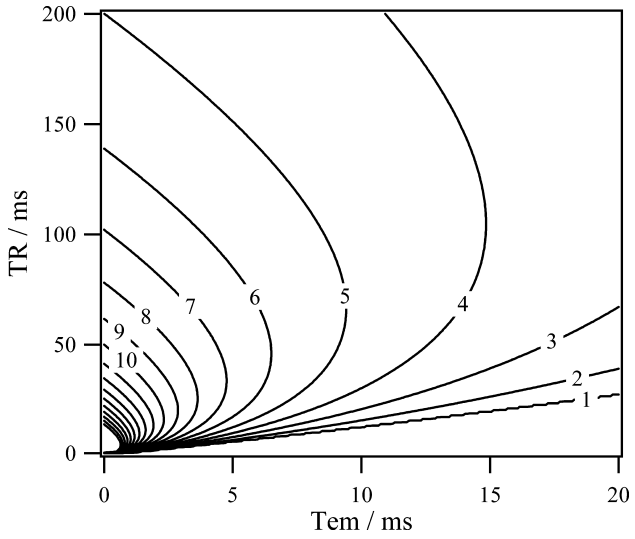

Fig. 2. Contour plot of the sensitivity enhancement E for MARYSE compared to partially saturated gradient echo signal obtained with Ernst angle as a function of Tem and TR. Simulations were performed for the water of the phantom ($T_1 = 2450$ ms; $T_2 = 550$ ms).

4.2. Effect of the relaxation time constants

To assess which kind of contrast and sensitivity enhancement E could be achieved with MARYSE under conditions of fast imaging, simulation of the normalized signal (Eqs. (1) and (3)) were carried out as a function of relaxation time constants, with Tem and TR values of 7 and 20 ms, respectively. Longitudinal relaxation time T_1 varied from 0 to 3000 ms and transverse relaxation time T_2 from 0 to 600 ms ($T_1 > T_2$). Fig. 3A reports the theoretical signal of the MARYSE sequence normalized to M_0. Fig. 3B shows the theoretical sensitivity enhancement E.

According to Eq. (1), signal was expected to be influenced by both T_1 and T_2 relaxation time constants. As illustrated in Fig. 3A, the higher signal was calculated for substances with long T_2 relaxation time and as short as possible T_1. Moreover in living systems and particularly at high magnetic field, T_1 is very high compared to T_2. Nevertheless, if a substance possesses a long T_2-value and a relatively long T_1-value e.g., water of our phantom ($T_1 = 2450$ ms; $T_2 = 550$ ms), its signal should be higher than signal of substances with short relaxation times like fat ($T_1 = 350$ ms; $T_2 = 45$ ms). For the phantom, theoretical values give a water/fat signal ratio of 1.45. Another consequence of this T_1 and T_2 weighting is illustrated in Fig. 3B, where the increase in SNR was obtained only for species with long T_2 values. In our phantom, signal enhancement was expected to be 4.6 for water and 1.2 for fat. This strong T_2-dependence shows an interesting use of the MARYSE sequence: in classical fast gradient echo imaging, substances with long T_1 are

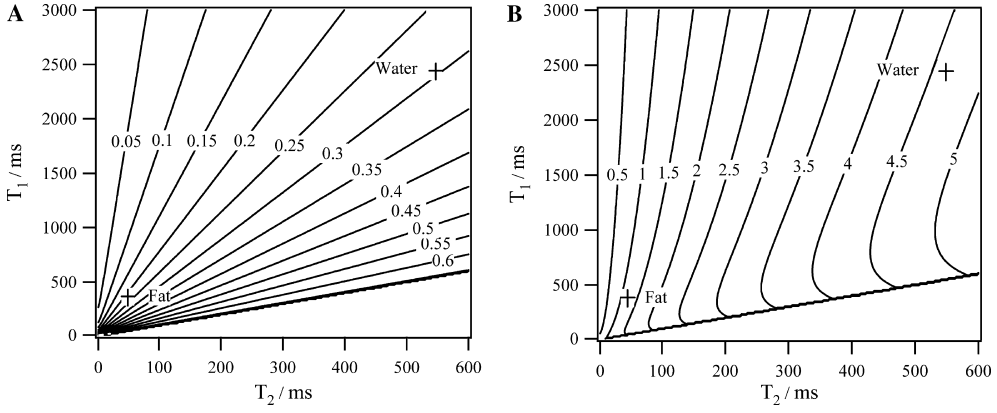

Fig. 3. (A) Contour plots of the MARYSE signal normalized to M_0 for a fixed Tem and TR (7 and 20 ms) as a function of relaxation time T_1 and T_2. (B) Contour plots of the signal enhancement E for a fixed Tem and TR (7 and 20 ms) as a function of relaxation time T_1 and T_2. Crosses (+) corresponded to relaxation time constants of water and fat.

saturated, a drawback partially compensated by the restoring pulse of MARYSE.

5. Results and discussion

Single slice 2D images were carried out on a water/fat phantom. The water signal-to-noise ratio obtained with MARYSE was compared to that measured with a standard gradient echo sequence using Ernst flip angle (with phase refocusing) and with fast spin-echo imaging (Fig. 4 and Table 1).

Fig. 4 shows the huge differences in signals originating from fat and water with respect to the pulse sequence used (MARYSE, Fast gradient echo or RARE). In MARYSE image (Fig. 4A), water appeared more intense than in the gradient echo image, as predicted from calculations reported in Fig. 3A. We also noticed a little signal reduction ($11 \pm 1\%$) between the first and the second echo of MARYSE (not shown) certainly due to T_2-damping. Despite a much longer acquisition time (15 min 52 s vs 1 min 22 s), water signal in RARE images was lower than signal recorded with MARYSE. This could be attributed to the effective echo time of 69 ms in the RARE sequence and to the role of the $90°_{-x}$ restoring pulse of MARYSE.

A seen in Fig. 4 the NMR signal of fat was lower in MARYSE and RARE images than in fast gradient echo image. On one hand fat has too short a T_2 relaxation time to be highly enhanced by MARYSE and on the other hand fat magnetization ($T_2 = 45$ ms) was damped in RARE imaging. Moreover, transverse magnetization was certainly sensitive to the crushing gradients located on both side of the refocusing pulse, thus explaining the loss of signal-to-noise ratio. The water/fat contrast-to-noise ratio was equal to 285 in MARYSE images (Table 1). When referring to the theoretical water/fat signal ratio of 1.45 (Fig. 3A), the expected CNR value was 117. This discrepancy could be attributed to different proton densities and to amplitude imperfections of the refocusing pulse with respect to fat magnetization, despite the large bandwidth of the hyperbolic-secant pulse.

Table 1
Signal-to-noise ratios (SNR) of water (outer region) and fat (inner region) and corresponding contrast-to-noise ratios (CNR) obtained with MARYSE, gradient echo, and RARE

	MARYSE	Gradient echo	RARE
Water SNR	378 ± 25	140 ± 11	178 ± 14
Fat SNR	93 ± 25	334 ± 11	78 ± 14
Water/fat CNR	285 ± 50	194 ± 22	100 ± 28

In order to measure the signal enhancement for water, TE1, TE2, and Tem were maintained at constant values (1.7, 5.3, and 7 ms). Signal-to-noise ratios were measured with MARYSE and a fast gradient echo sequence with a nutation angle optimized for water, on a 5-mm diameter water tube placed at the center of the coil. Repetition time varied from 12 to 200 ms (Fig. 5). The curve shape of the measured signal enhancement as a function of TR was comparable to the theoretical curve but experimental values were slightly lower. The maximum measured enhancement value was 5.1 in the first echo for a repetition time of 50 ms. Maximal theoretical value is 5.3. This small difference could be partly

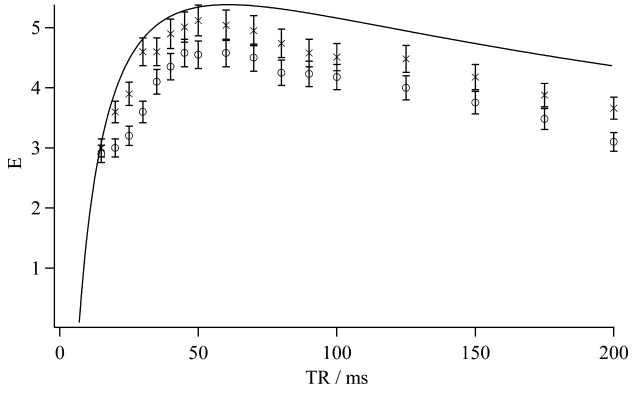

Fig. 5. Theoretical (solid line) and experimental values (× first echo and ○ second echo) of signal enhancement E for water obtained with MARYSE compared to a gradient echo with Ernst flip angle. Measurements errors are estimated to 5%.

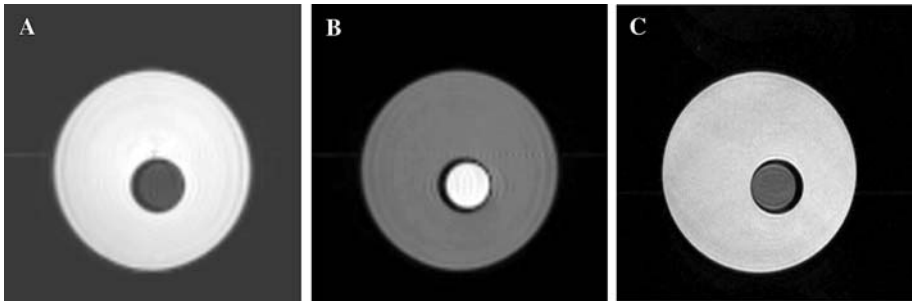

Fig. 4. (A) Axial images of the fat/water phantom (vial of vegetable oil inserted in a cylinder filled with water) obtained with MARYSE first echo (TR/TE/Tem = 20/1.7/7 ms). (B) Gradient echo image using optimized nutation angle for water (TR/TE = 20/1.7 ms). (C) RARE image (TR/TE_{eff} = 3718/69 ms).

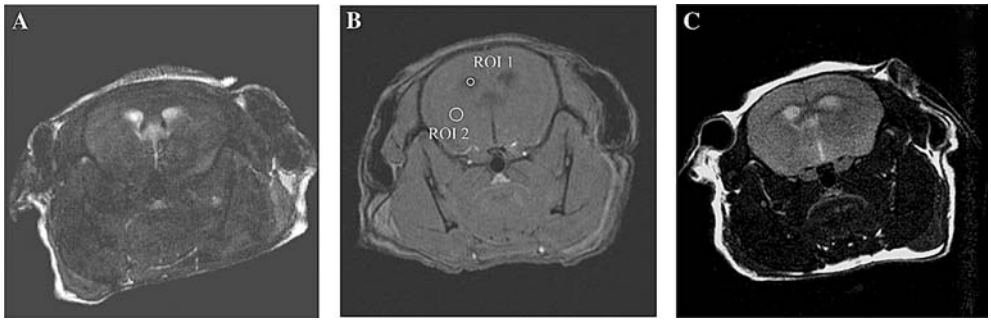

Fig. 6. Central partition of a 3D image of the mouse head obtained with: (A) MARYSE (TR/TE/Tem = 20/1.7/7 ms) and (B) gradient echo (TR/TE = 20/1.7 ms). (C) 2D slice of the mouse head obtained with RARE ($TR/TE_{eff} = 3718/69$ ms).

due to gradients and particularly crushers on both sides of refocusing 180° pulse. They probably reduced transverse magnetization that was restored along the longitudinal axis. Nevertheless crushers were necessary to spoil unwanted coherences. Another cause that might explain the small theory vs experiment discrepancy was the sensitivity of MARYSE to radiofrequency field heterogeneity. As a matter of fact higher enhancements were measured in thin tubes positioned at the very center of the birdcage coil. In this area, B_1 radiofrequency field was very homogeneous. On the contrary lower signal enhancements (maximum 2.7, see Table 1) were recorded in the 20 mm phantom with poorer RF homogeneity. Confirmation of the crucial role of the refocusing pulse in MARYSE was brought by separate experiments. It was found that the NMR signal decreased by a factor of 0.8 when pulse nutation angle varied by 20° (not shown).

5.1. Animal studies

To evaluate the usefulness of the MARYSE sequence, images of the mouse brain were achieved. They were compared to images obtained with gradient echo and RARE. MARYSE and gradient echo images were acquired with the same resolution and the same acquisition time whereas 2D images were obtained with RARE.

As seen in Fig. 6A, in MARYSE images only CSF in the ventricles gave a very intense signal in the mouse brain. The other brain tissues possessed too short T_2s (50 ms) to be enhanced. The simulation for *basal ganglia* of the rat brain ($T_1 \approx 1000$ ms and $T_2 \approx 50$ ms) [19] gives a value for E equal to 0.9. With gradient echo sequence (Fig. 6B), CSF was significantly saturated and signal from the rest of the brain was uniform. With RARE (Fig. 6C), signal from liquid was also more intense than other brain tissues but the image contrast between CSF and surrounding tissues was lower than with MARYSE. Table 2 reports the signal-to-noise ratio of CSF (ROI 1 in Fig. 6B) and brain tissues (ROI 2) obtained with MARYSE, gradient echo, and RARE and the corresponding contrast-to-noise ratios.

Table 2
Signal-to-noise ratios (SNR) of CSF and brain tissues and corresponding contrast-to-noise ratios (CNR) obtained with MARYSE, gradient echo, and RARE on mouse brain

	MARYSE	Gradient echo	RARE
CSF (ROI 1) SNR	18.8 ± 1.5	7.1 ± 1.7	11.5 ± 1.6
Brain tissues (ROI 2) SNR	4.6 ± 1.5	13 ± 1.7	8.9 ± 1.6
CSF/brain CNR	14.2 ± 3	5.1 ± 3.4	2.6 ± 3.2

Regions of interest (ROI 1 and ROI 2) are indicated in Fig. 6B.

As expected from the theoretical calculations, CSF signal was well enhanced with MARYSE compared to other sequences. On the contrary, a significant signal decrease was observed in the other parts of the brain. This is why the contrast between CSF and other tissues with MARYSE was higher (Table 2). In that way, a segmentation of the liquid was easy to carry out. MARYSE images were reconstructed as $256 \times 256 \times 256$ matrix, brain extraction and then segmentation was applied. Most of the CSF volume could be reconstructed (not shown, an example can be accessed at http://www.rmsb.u-bordeaux2.fr/rmsb/Personnel/Sylvain). Only small areas of the ventricles were sometimes not clearly visible, certainly due to very small thickness (<200 μm).

5.2. Specific absorption rate considerations

As MARYSE was designed with additional π and π/2 pulses care must be taken with respect to excess of electromagnetic power deposition. A simplified expression for absorbed power P_{abs} is the following:

$$P_{abs} \approx P_{tot}\left(1 - \frac{Q_{loaded}}{Q_{free}}\right) D_C \eta \quad (4)$$

with P_{tot} the total electromagnetic power emitted by the RF coil, Q_{loaded} and Q_{free} the quality factors of loaded and unloaded coil, respectively, D_C the duty cycle of RF emission, and η the filling factor of the RF coil. Attributing $P_{tot} = 15$ kW (i.e., the maximal power available on

common standard 1.5 T MRI systems and assuming that all the electric power is converted into electromagnetic waves), $Q_{\text{loaded}}/Q_{\text{free}} = 0.9$, $D_C = 0.1$ (e.g., two 90° pulses lasting 500 μs and one 180° pulse lasting 1 ms with TR = 20 ms), and $\eta = 0.3$ ($\eta = 0.5$ for a fulfilled solenoid coil) and for a human body mass of 50 kg the specific absorption rate (SAR) value is 0.9 W/kg. Even though calculated for extreme power emission this value remains reasonable. As a comparison a True-Fisp sequence with TR = 1.7 ms and pulse length of 300 μs would exhibit a SAR of about 1 W/kg for low nutation angle. Moreover MARYSE ran successfully on a 0.2 T open magnet system (Siemens, Erlangen, Germany) under manufacturer SAR supervision.

In vitro and in vivo images show the interest of MARYSE for fast imaging of liquids: restoring the transverse magnetization along the longitudinal axis permitted to increase artificially the R_1 relaxation rate and consequently increase the signal. Even though the efficiency of MARYSE is linked to the quality of the 180° refocusing pulse, in vitro results showed that an enhancement of the water signal by a factor of 5.1 (increase of temporal resolution around 26) could be expected. One of the disadvantages of fast imaging at high static magnetic field (T_1 saturation of liquids) could in that way be partially compensated while conserving several advantages brought by gradient echo (3D imaging, fast acquisition). Results obtained in vivo showed that a significant contrast at high field could be generated between liquid and other tissues. If two gradient echoes were recorded within a single repetition time the corresponding increase in SNR would enable high resolution imaging. As the restoring pulse is applied to a spin-echo the sensitivity enhancement is not much influenced by static field inhomogeneities. Its makes the sequence useful at high field, particularly for NMR microscopy.

A possible and interesting application of MARYSE would be the detection of tumors. Tumors are very vascularized areas that usually possess longer relaxation time values than surrounding healthy tissues. MARYSE could enhance tumor signal for a better detection without the use of contrast agents like Gadolinium. Finally a flow-compensated MARYSE sequence would be useful for detection of moving liquids. In such a case an angiographic application of this new sequence might be considered as well.

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