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NOTE

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Compressed-Sensing MP2RAGE sequence: Application to the detection of brain metastases in mice at 7T

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Purpose: To develop a Compressed Sensing (CS)-MP2RAGE sequence to drastically shorten acquisition duration and then detect and measure the T_1 of brain metastases in mice at 7 T.

Methods: The encoding trajectory of the standard Cartesian MP2RAGE sequence has been modified (1) to obtain a variable density Poisson disk under-sampling distribution along the k_y-k_z plane, and (2) to sample the central part of the k-space exactly at TI_1 and TI_2 inversion times. In a prospective study, the accuracy of the T_1 measurements was evaluated on phantoms containing increasing concentrations of gadolinium. The CS acceleration factors were increased to evaluate their influence on the contrast and T_1 measurements of brain metastases in vivo. Finally, the 3D T_1 maps were acquired with at 4-fold increased spatial resolution. The volumes and T_1 values of the metastases were measured while using CS to reduce scan time.

Results: The implementation of the CS-encoding trajectory did not affect the T_1 measurements in vitro. Accelerating the acquisition by a factor of 2 did not alter the contrast or the T_1 values of the brain metastases. 3D T_1 maps could be obtained in < 1 min using a CS factor of 6. Increasing the spatial resolution enabled more accurately measurement of the metastasis volumes while maintaining an acquisition duration below 5 min.

Conclusion: The CS-MP2RAGE sequence could be of great interest in oncology to either rapidly obtain mouse brain 3D T_1 maps or to increase the spatial resolution with no penalty on the scan duration.

KEYWORDS
compressed sensing, metastases, MP2RAGE, mouse brain, 7T

1 | INTRODUCTION

Metastases are the major cause of death of cancer patients. Longitudinal relaxation time T_1 mapping has shown great promises in the detection and characterization of metastases.[1,2] 3D T_1 mapping at high resolution would allow identification of early growing metastases and limit partial volume effects on the T_1 and the volume measurements. Among T_1 mapping sequences, very few are carried out in 3D because of prolonged acquisition times, which are incompatible in the clinical settings or for scanning large cohorts of animals in preclinical studies. Interestingly, the MP2RAGE sequence provides 3D T_1 maps in a reasonable scan time.[3] It has also shown great potential in human brain imaging because of the high contrast it provides between brain structures, especially at high clinical magnetic field strengths.[4–6] Similarly in mice,

it has been used to obtain T_1 structural brain imaging following Manganese injection.

Unfortunately, the current MP2RAGE sequence required 10 min to image the whole human brain at 1 mm isotropic resolution and 31 min to obtain 156 μm isotropic mouse brain T_1 maps. These durations are still too long for it to be routinely applicable in either the clinic or preclinical studies. Consequently, there is a need to accelerate the 3D MP2RAGE sequence. A common method is to combine it with parallel imaging.[3,4,7] The common use of receive arrays with a limited number of channels prohibits the efficiency of this approach in preclinical studies. Another way to reduce acquisition time is the compressed sensing (CS) technique. It relies on the sparsity of the data within the k-space. Compared to parallel imaging, the amount of receiver coils is not a limitation. The CS technique is still largely unused on small animals. To date, only two studies combined it with T_1-parametric sequences[8,9] but only to obtain 2D maps.

To our knowledge, human MP2RAGE data have only been reconstructed with the CS technique retrospectively.[10] To prospectively accelerate the acquisition, specific encoding schemes need to be developed to fit the characteristics of this sequence.

The goal of our study was to develop a MP2RAGE sequence with a specific k-space encoding to enable the CS technique. This CS-MP2RAGE was used to prospectively reduce the acquisition time of mouse brain T_1 maps to detect brain metastases. Then, this CS-MP2RAGE sequence was used to increase the spatial resolution of the mouse brain T_1 maps without lengthening acquisition time. It therefore enabled to detect early growing brain metastases and measure their corresponding T_1.

2 | METHODS

2.1 | MP2RAGE sequence

A Cartesian MP2RAGE sequence as described by Marques et al[3] (Supporting Information Figure S1A) was implemented and called "Fully" thereafter. TI_1 and TI_2 are the two inversion times where the center of the k-space of the two gradient echo blocs (GRE) positioned in respect to the center of the inversion pulse. The delay between the inversion pulse and each echo of the GRE block is indicated as $TI_{e(n)}$ (TI_{e1} to TI_{e128}).

2.2 | CS-undersampled acquisition strategy

The encoding trajectory of this standard Cartesian MP2RAGE sequence has been modified (1) to obtain a variable density Poisson (VDPoisson) disk undersampling distribution along the k_y-k_z plane,[11,12] and (2) to sample the central part of the k-space exactly at the two inversion times. The method is described in detail in Supporting Information Figure S1B.

Figure 1A illustrates the first 4 $MP2RAGE_{TR}$ encoding trajectories acquired with the proposed method. Their combination enables a CS acceleration factor of 4 in this case. Each region along the k_y-axis is sampled at the same effective TI_e (see color scale).

As shown in Figure 1B, by fixing the echo train length per GRE readout and decreasing the number of $MP2RAGE_{TR}$, the VDPoisson method concentrates the echoes at the center of the k-space. Consequently, a broader range of effective TI_e is located at the middle of the k_y-axis, depending on the acceleration factor. Figure 1C represents the TI_e as a function of the echo number in the gradient echo train, for Fully and accelerated acquisitions. TI_e is linear for the Fully acquisition and follows a sigmoid curve for the CS acquisitions. The slope at the inflexion point increases with the acceleration factor.

Simulations of the point spread function (PSF) have been performed without or with a CS ×4 acceleration factor. It showed the influence of the T_1 value on the PSF using a standard MP2RAGE. The new encoding scheme only resulted in a broadening of these PSF by 10% and 17% for a substance with T_1 of 1300 and 2000 ms, respectively (Supporting Information Figure S2).

All the images acquired with the MP2RAGE sequence combined with the CS acceleration were obtained prospectively using the above encoding strategy.

2.3 | Magnet and gradient system

Experiments were performed on a 7 T Bruker BioSpec system (Ettlingen, Germany) equipped with a volume resonator (75.4 mm inner diameter, active length 70 mm) for excitation, and a 4-element (2 ×2)-phased array surface reception coil (outer dimensions 26 ×21 mm^2).

2.4 | Cell culture and animal models of brain metastases

The human breast cancer cell line (MDA-MB-231Br) was cultured in Dulbecco's modified Eagle's medium (Invitrogen) containing 10% fetal bovine serum at 37°C and 5% CO_2.

All experimental procedures were approved by the local Animal Care and Use Institutional ethics committee of Bordeaux, France (CEEA50, approval 5012032-A).

Female nu/nu mice ($N = 5$; 8 weeks old; Charles River Laboratories, L'Arbresle, France) were injected into the left ventricle of the beating heart with 100 μL suspension of 150,000 MDA-MB-231Br cells. Mice were scanned biweekly from day 21 post-injection.

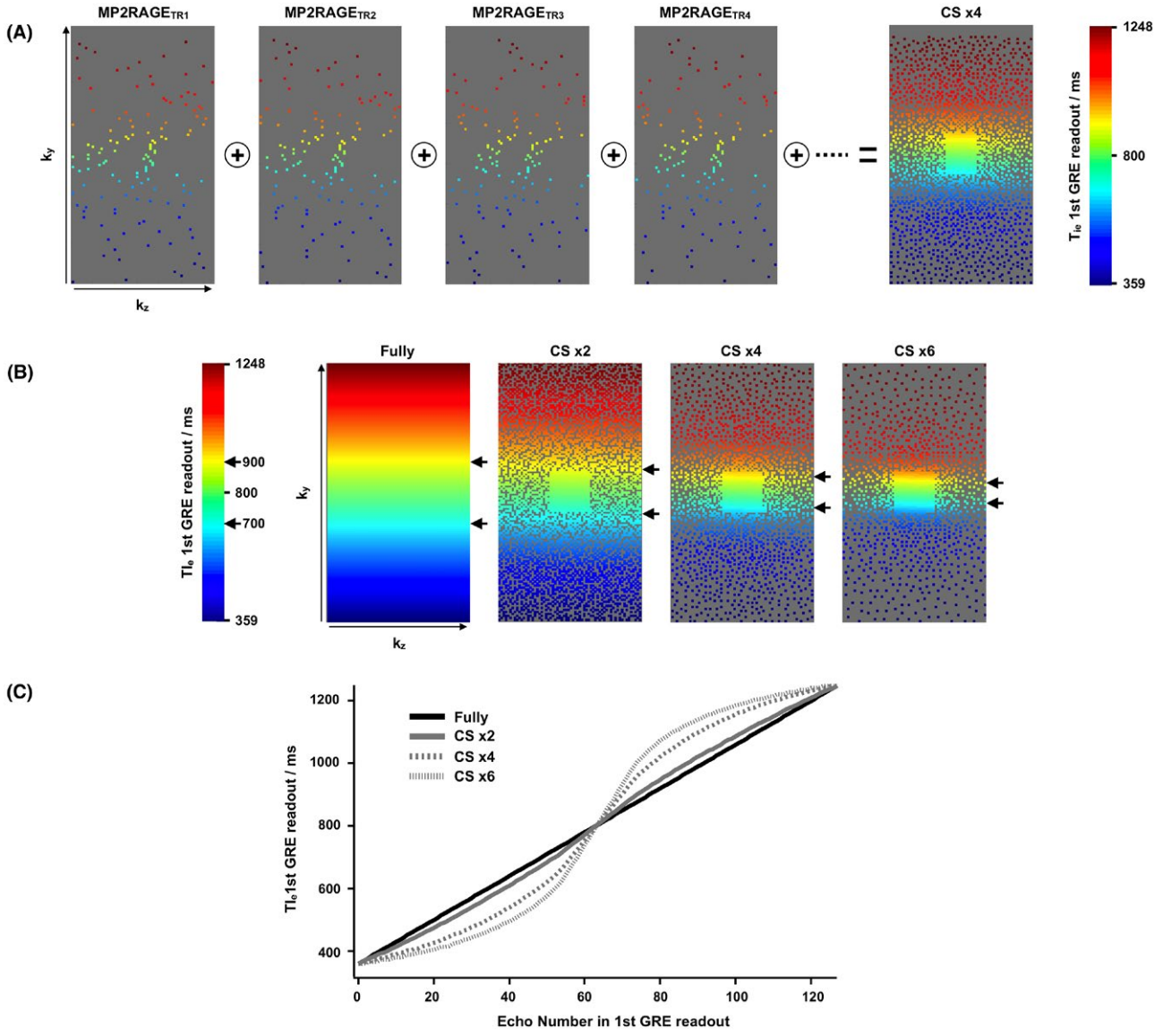

FIGURE 1 **(A)** Encoding trajectories within the k-spaces for a CS-MP2RAGE sequence with an acceleration factor of 4. The trajectories in the k_y-k_z plane during the first four MP2RAGE$_{TR}$ and their combination are shown. The example of the first GRE readout (set at TI_1 value of 800 ms) is shown. $TI_{e(n)}$ within the 1st GRE readout are color-encoded (see color scale). **(B)** Effect of the CS acceleration factors (×2, ×4, and ×6) on the TI_e position in the k-space. The example of the first GRE readout (set at TI_1 value of 800 ms) is shown. The arrows point at TI_e = 700 and 900 ms to show the increasing concentration of the TI_e at the center of the k-spaces. **(C)** Curves of TI_e as a function of the echo number in the GRE readout, for Fully and accelerated acquisitions

2.5 | In vitro experiments

A phantom containing vials with 46-216 μM of Gd-DTPA (ProHance) in physiological serum was prepared (generating T_1 values from 792-1979 ms) to evaluate the T_1 measurements accuracy using the CS-MP2RAGE sequence. Six independent experiments were conducted.

2.6 | In vivo experiments

Mice were anesthetized with isoflurane (1.5-2% in air) and positioned with the brain at the center of the NMR coil. Animal breathing was monitored during the scanning session (SA Instruments, Stony Brook, NY).

2.7 | Imaging parameters

The MP2RAGE parameters were as follow: TI_1/TI_2/MP2RAGE$_{TR}$ = 800 ms/2200 ms/6250 ms; FOV = 25 × 20 ×18 mm; flip angle = 7°; number of points in the central part of the k_y-k_z plane = 20 × 18; 128 echoes per GRE readout.

A low spatial resolution set (noted LR thereafter) with matrix = 128 × 128 ×64 was used with the following parameters: TE/TR = 3.253/7 ms; receiver band width (rBW) =

232.5 Hz/pixel; 6 min 40 s. Combined with CS ×2, CS ×4, and CS ×6, the duration was shortened to 3 min 20 s, 1 min 40 s, and 50 s, respectively.

A second set of acquisitions was performed with high spatial resolution (noted HR thereafter): matrix = 192 × 160 ×128; TE/TR = 3.072/8.056 ms; rBW = 260.4 Hz/pixel; scan time: 16 min 42 s, 8 min 07 s, and 4 min 16 s when Fully or combined with CS ×2 and CS ×4, respectively.

For the in vitro experiments, reference T_1 were measured using an inversion-recovery (IR) sequence: 120 TI acquired every 100 ms, from 100 to 12,000 ms; TE/TR = 10 ms/15 s; FOV: 25 ×18 mm; matrix: 128 ×64; rBW = 781 Hz/pixel; slice thickness = 2 mm, scan time = 8 hours.

2.8 | Reconstruction

The CS encoding scheme was used to perform a L1-ESPIRiT[13] reconstruction with L1 wavelet regularization (W) and total variation (TV) on both TI images. This ESPIRiT-based parallel imaging and CS reconstruction was performed using the Berkeley Advanced Reconstruction Toolbox (BART, DOI:10.5281/zenodo.592960). Estimation of the coil sensitivity was performed using ESPIRiT calibration. Multiple values of W and TV parameters were tested. The number of iteration was set to 60.

2.9 | Image analysis

TI_1 and TI_2 images were combined to provide the MP2RAGE image.[3] The 3D T_1 maps were reconstructed according to the MP2RAGE relationship using in-house MATLAB software (The MathWorks, Natick, MA).

Regions of interest (ROI) were manually drawn around 88 metastases (present within 5 mice, scanned at different time points), the cortex, and several head structures on the LR Fully and CS (×2, ×4, ×6) T_1 maps. The mean T_1 values were measured as the mean of the values of each voxel within the ROI. The contrast of the metastases was measured as the difference in T_1 values between the metastases and the surrounding healthy brain. The CNR calculation from Marques et al[3] could not be applied in our case, as the CS technique virtually alters noise intensity. In addition, the T_1 of each metastasis was individually compared between the LR Fully, LR + CS ×2, LR + CS ×4, and LR + CS ×6.

In parallel, the volumes of 12 metastases were measured through ROIs manually drawn on every slice where the metastases could be detected on the HR Fully MP2RAGE images, HR + CS ×2, HR + CS ×4, and the LR Fully MP2RAGE images, using Amira software (TGS, San Diego, CA). The T_1 of the metastases were also measured using the corresponding T_1 maps. This analysis was performed by three independent observers.

2.10 | Statistical analysis

The T_1 values, the volumes and the metastasis contrasts were compared using a one-way ANOVA test followed by the Bonferroni posttest (GraphPad Prism 5.0). A P-value < 0.05 was considered to be statistically significant.

3 | RESULTS

In vitro experiments demonstrated that the T_1 values of each Gd-DTPA concentration were not different between the MP2RAGE Fully and acceleration factors of 2, 4, and 6 and the IR sequence (Supporting Information Figure S3).

Figure 2 shows the TI_1, TI_2, and MP2RAGE images of a mouse brain bearing breast cancer-derived brain metastases acquired with Fully and CS ×2 reconstruction.

The impact of TV and W weighting factors on image quality is illustrated; a decrease in noise and smoothing of spatial features were observed in the CS ×2 images with increasing regularization. TV and W were chosen at 0.0001 and 0.01, respectively, to facilitate metastases identification. Using the chosen parameters set, brain metastases were detected as hyper-intense areas on GRE_{TI1} and as hypo-intense areas on the GRE_{TI2} and the MP2RAGE images.

The influence of applying increasing CS factors on the detection of brain metastases was evaluated on LR MP2RAGE images and T_1 maps (Figure 3). Early growing metastases were clearly detectable both on the Full data set and on the CS ×2 images (dashed arrow), despite the reduced acquisition time of the latter (6 min 40 s and 3 min 20 s, respectively). Metastasis detection got hampered for CS of 4 and 6. These observations were confirmed by the quantitative analyses of the T_1 maps. The contrast of the metastases on the T_1 maps was similar on the Fully sampled T_1 map and on the CS ×2 T_1 map. However, the metastasis contrasts decreased when applying CS ×4 and CS ×6 ($P < 0.05$ and $P < 0.01$, respectively).

The mean T_1 of more than 80 metastases was similar on the LR Fully and CS ×2 T_1 maps (Table 1). This value decreased by a maximum of 6% when CS ×4 and CS ×6 were applied ($P = 0.007$ and $P = 0.0005$, respectively). It is important to note that the T_1 of the cortex, hippocampus, cerebellum (white matter), and olfactory bulbs did not significantly vary between the Fully data set and all the CS ones. For tissues with very long (ventricles, aqueous humor) or very short (lens) T_1 values, the CS factor could influence the measurements.

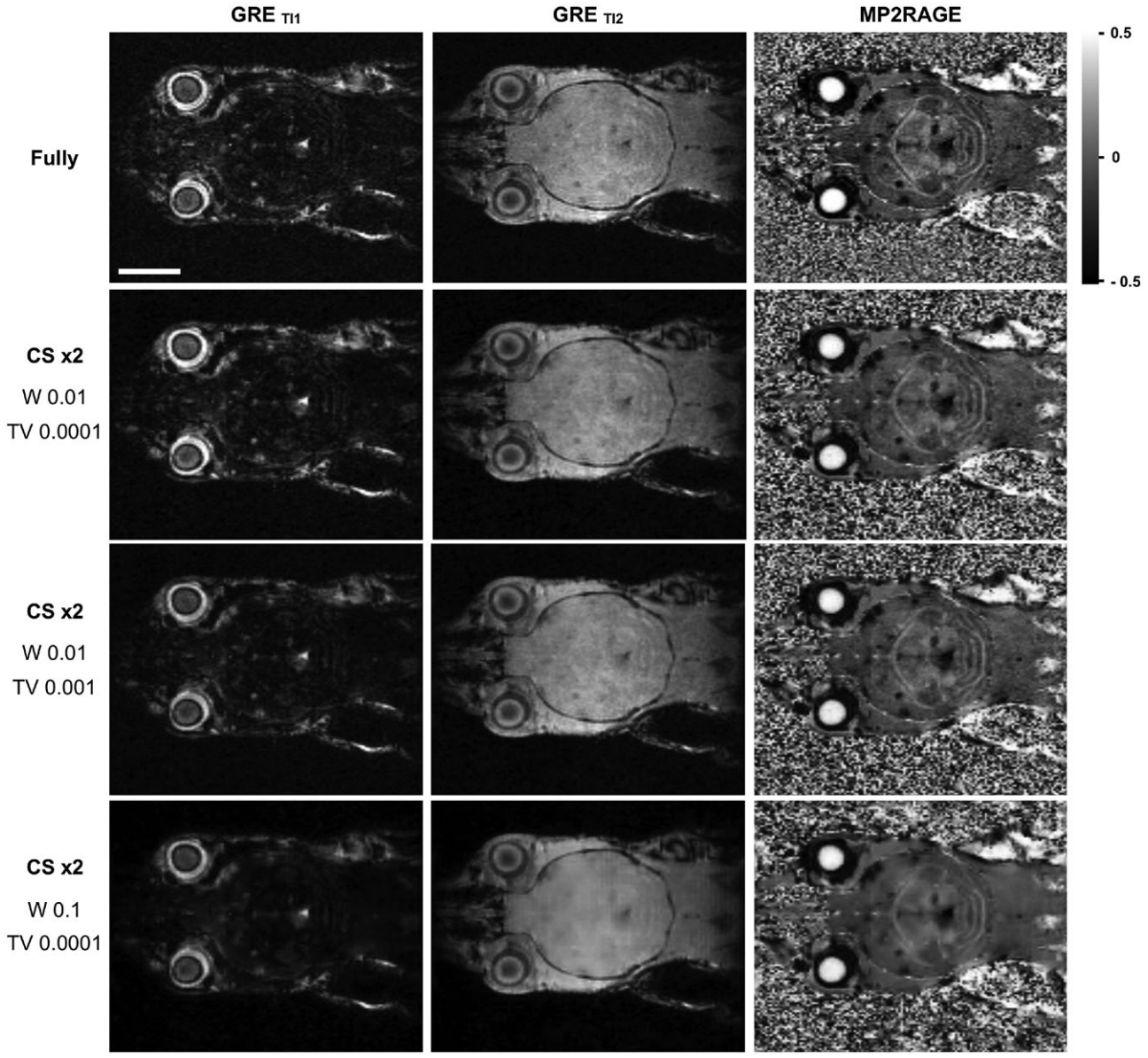

FIGURE 2 Coronal views of the two images acquired at the 2 TI (GRE_{TI1} and GRE_{TI2}) and the combined MP2RAGE images acquired on a mouse brain bearing brain metastases. The images were acquired with LR full data set (Fully) and prospectively under-sampled with a CS factor of 2 (CS ×2). Different total variation (TV) and wavelet (W) weighting factors are shown. Acquisition times were < 7 min and < 3.5 min for the Fully and CS ×2 acquisitions. Scale bar, 0.5 mm.

Finally, the CS technique was used to increase the spatial resolution by 4 without lengthening acquisition time (Figure 4). The measured metastasis volume was on average 45% lower in HR images compared to LR data sets ($P < 0.0001$). In addition, some early growing metastases that were hardly detectable on LR images were easily distinguished from healthy brain tissue on the HR images (arrows). The metastasis volumes were similar in the HR Fully data set and in the HR + CS images. No significant difference was measured on the T_1 values of the metastases between the different sequences used. Consequently, the HR + CS × 4 images and T_1 maps were of better quality, more informative, and faster to acquire than the LR Fully T_1 maps.

4 | DISCUSSION

This article proposes the acceleration of the MP2RAGE sequence acquisition for the detection of brain metastases in mice. For the sequence to be compatible with the CS technique, a specific encoding trajectory had to be implemented to accommodate the dual inversion time acquisition. The CS-MP2RAGE sequence enabled to increase image quality by decreasing noise and/or increasing spatial resolution while shortening acquisition time. This study showed that applying the CS technique did not affect in vitro T_1 measurements. Even though the $MP2RAGE_{TR}$ was set at 6.2 s to

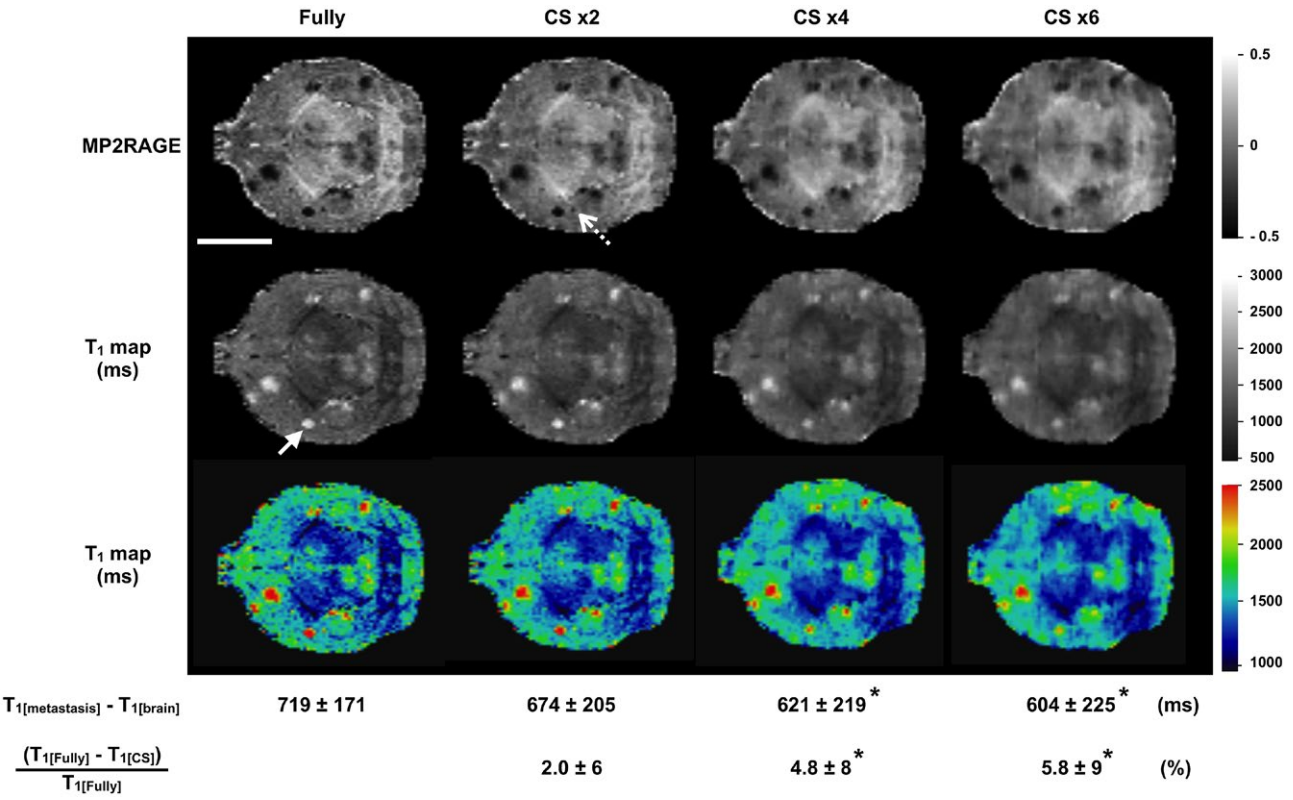

FIGURE 3 MP2RAGE images and the corresponding T_1 maps (coronal views) of a mouse brain bearing brain metastases acquired with LR full data set and with increasing CS factors (×2, ×4, ×6). Acquisition times were < 7 min, <4 min, <2 min, and <1 min, respectively. The last row shows the same T_1 maps with a narrow color scale to better appreciate the effect of CS undersampling on the T_1 values throughout the brain. The arrows point at two separate metastases. The contrast of the metastases measured on the T_1 maps (called T_1[metastasis]-T_1[brain]) and their difference in T_1 values between the Fully data set and the CS ones (T_1[Fully] − T_1[CS])/T_1[Fully]) are shown under each corresponding image. Scale bar, 0.5 mm. *$P < 0.05$ compared to Fully.

TABLE 1 T_1 values measured with the MP2RAGE sequence with the full data set (Fully) and acceleration factors of 2, 4, and 6 (CS ×2, CS ×4, CS ×6, respectively) on several healthy brain structures and on a population of 88 metastases

T_1/ms	Metastases	Cortex	Hippocampus	cerebellum WM	olfactory bulb	ventricle	Head muscle	Aqueous humor	Lens
Fully	2240 ± 184	1516 ± 55	1508 ± 32	1535 ± 52	1639 ± 22	2502 ± 77	1382 ± 9	2407 ± 96	576 ± 35
CS x2	2197 ± 213	1509 ± 52	1505 ± 35	1480 ± 74	1603 ± 53	2264 ± 80*	1365 ± 16*	2476 ± 112	566 ± 43
CS x4	2132 ± 230*	1490 ± 60	1507 ± 55	1481 ± 62	1614 ± 47	1993 ± 102*	1379 ± 25	2539 ± 138*	597 ± 70
CS x6	2109 ± 240*	1461 ± 89	1477 ± 98	1438 ± 108	1558 ± 97	1779 ± 80	1352 ± 72	2575 ± 122*	645 ± 72*

*$P < 0.05$ compared to Fully.

maximize the acceleration of the MP2RAGE sequence, it could be lengthened to accommodate for imaging at high magnetic fields. Nonetheless, the T_1 of the mouse brain cortex and metastases measured in vivo were similar to the wide range of values found in the literature[14–18] and were not modified when applying CS. In the case of very small structures, spatial smoothing can occur and affect the measurements.

Although the MP2RAGE sequence is often used for multiple sclerosis detection in humans, it has not been applied in oncology. For the first time, our study demonstrates the use of the MP2RAGE sequence to obtain high brain metastasis contrast in mice. Acceleration through the CS technique enabled the maintenance of this contrast even though, when acceleration factors were higher than 2, this contrast tends to decrease because of the regularization method used during the reconstruction of the images. Nonetheless, because of large T_1 values differences, the contrast of the metastases with healthy brain was still high enough to easily detect metastases throughout the whole brain in < 1 min (CS ×6).

In parallel, the CS technique can also be used to increase the spatial resolution without majorly lengthening acquisition

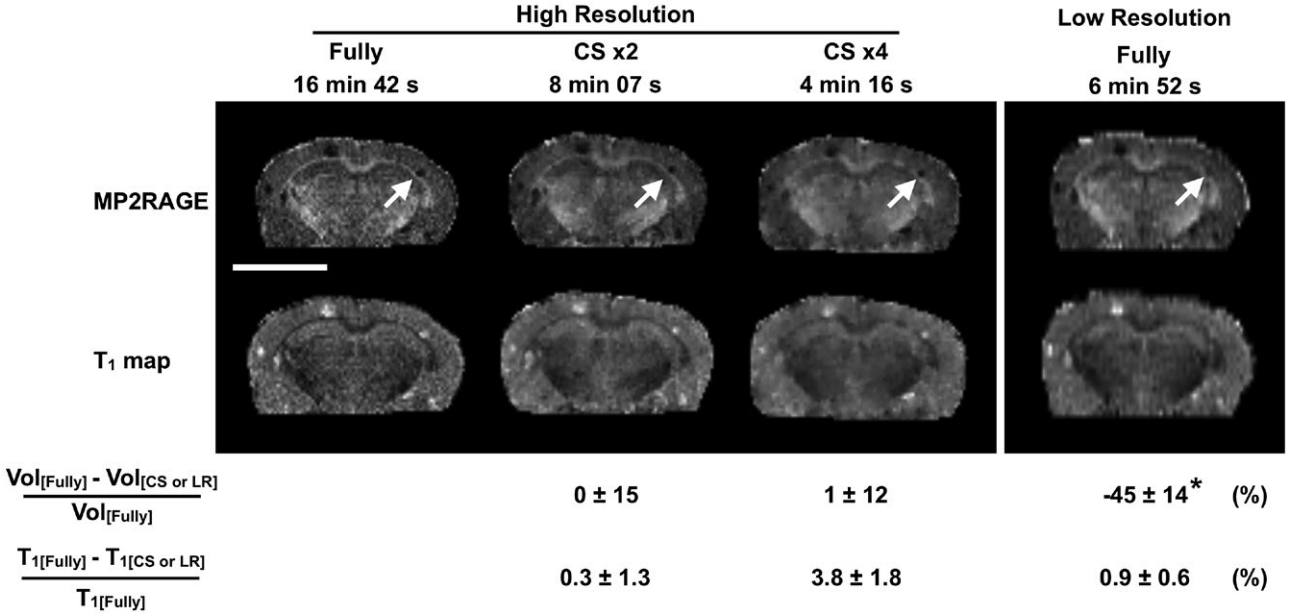

FIGURE 4 MP2RAGE images and the corresponding T_1 maps (axial views) of a mouse brain bearing brain metastases acquired with LR full data set, HR full data set, and with increasing CS factors (×2, ×4). The arrow points at 1 early growing metastasis that can hardly be detectable on the LR images but is easily detectable on the HR + CS images in shorter acquisition times. The difference in metastasis volume and T_1 values between the HR Fully data set and the CS ones or the LR data set (Vol[Fully] − Vol[CS or LR])/Vol[Fully] and (T_1[Fully] − T1[CS or LR])/T_1[Fully], respectively) are shown under each corresponding image. Scale bar, 0.5 mm. *$P < 0.05$

duration. This approach has already been used for DCE imaging in rats.[19] In our case, the spatial resolution of the images was increased to facilitate the detection of early growing metastases that have small diameters and to more accurately measure their volumes. Indeed, metastases covering < 10 voxels and representing volumes of < 0.023 mm^3 were detected. On these small structures, T_1 values were also measured. Therefore, the CS-MP2RAGE sequence would be relevant for longitudinal studies of large cohorts of animals, where acquisition time is crucial and for evaluating the efficiencies of innovative therapies.

The first limitation of this study is inherent to the use of the MP2RAGE sequence, as it involves the setting of the sequence parameters with an a priori knowledge of the T_1 of the pathology of interest. In oncology, metastases and tumors usually have longer T_1 than healthy tissues because of high vascularity and the presence of edema. A setting similar to the one used in human studies,[20] enables the measurement of a wide range of T_1 values. Consequently, the images obtained in our study generated enough contrast to detect the brain metastases. Second, even though the MP2RAGE sequence has been shown to be sensitive to B_1,[3] our acquisition set-up containing a large transmit coil compared to the sample size should maintain a high B_1 homogeneity in the mouse brain.

Another limitation relies on the CS technique. The CS parameters used for the reconstruction were chosen empirically and the same parameters were used for both TI images. Consequently, further optimization considering alternative CS priors and adaptive weightings is warranted to improve the contrast and delineation of the metastases.

In addition, the CS-encoding strategy concentrates the echoes at the center of the k-space which affects the PSF peak, depending on the T_1 value. This partially explains the image deterioration with the CS technique. Nonetheless, the standard MP2RAGE sequence already modifies the PSF.

The CS-MP2RAGE sequence can be improved to demonstrate its potential for other applications, such as imaging respiration affected regions (using radial sampling)[21] or dynamic imaging.[22]

5 | CONCLUSION

In conclusion, the MP2RAGE acquisition can be drastically shortened by benefiting from the proposed CS technique implementation. This can be used either to reduce acquisition duration or to increase spatial resolution without lengthening scan time to increase the sensitivity for small structure detection in small animals at high magnetic fields. This method can also be easily transferred to human imaging and would further benefit from its combination with parallel imaging.[23] The MP2RAGE sequence could therefore become a routine sequence in clinic.

ACKNOWLEDGMENTS

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

FIGURE S1 (A) Chronogram of the MP2RAGE sequence. TI_1 and TI_2 are the delays between the RF pulse and the echo recorded at the center of the k-space, of the 1st and the 2nd GRE readouts, respectively. TI_{e1}, TI_{e2} ,…, TI_{e128} are the times from the RF pulse and the 1th to 128th echoes recorded. (B) Steps to create the CS-MP2RAGE encoding trajectory. (1) Generation of the VDPoisson mask in the k_y-k_z plane using the E-SPIRiT toolbox developed by Uecker et al[13]. The number of mask point (NMP) generated has to be dependent on the CS acceleration factor and a multiple of the number of echoes per GRE readout. (2) For each point of the mask, recording of the encoding coordinates (k_{y1}, k_{y2}, … and k_{z1}, k_{z2},…) and ordering starting from the bottom left part to the top right part of the k-space. (3) Reordering of the coordinates to create different encoding trajectories for each $MP2RAGE_{TR}$. The list of points was then divided in $Nset = Nmask/GRE_n$ so that, for each $MP2RAGE_{TRi,}$ an encoding trajectory was created as follow: [i, $i + NMP/GRE_{n,}$ $i + 2 * NMP/GRE_n$, …, $i + (GRE_{n-1}) * NMP/GRE_n$]. The

example of a matrix size of 128 ×64 and an acceleration factor of 2 is presented.

FIGURE S2 Simulated point spread function (PSF) for two tissues with $T_1 = 1300$ ms (top) and 2000 ms (bottom) and $T_{I1} = 800$ ms obtained for a standard MP2RAGE sequence (blue) and a CS ×4 MP2RAGE sequence (red). The corresponding measurements of the full width at half maximum (FWHM) are shown.

FIGURE S3 T_1 values measured with the MP2RAGE sequence with the full data set (Fully) and acceleration factors of 2, 4, and 6 (CS ×2, CS ×4, CS ×6, respectively) on tubes containing increasing concentrations of Gd-DTPA. The values were compared to the gold-standard inversion recovery measurements.

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