Published in final edited form as:

Magn Reson Med. 2015 May ; 73(5): 1786–1794. doi:10.1002/mrm.25298.

Optimization of White-Matter-Nullled Magnetization Prepared Rapid Gradient Echo (MP-RAGE) Imaging

Manojkumar Saranathan, PhD¹, Thomas Tourdias, MD, PhD¹, Ersin Bayram, PhD², Pejman Ghanouni, MD¹, and Brian K. Rutt, PhD¹

¹Department of Radiology, Stanford CA USA

²Applied Science Laboratory, GE Healthcare, Waukesha WI USA

³Department of Neurology and Neurological Sciences, Stanford CA USA

Abstract

Purpose—To optimize the white-matter-nullled (WMn) Magnetization Prepared Rapid Gradient Echo (MP-RAGE) sequence at 7T, with comparisons to 3T.

Methods—Optimal parameters for maximising SNR efficiency were derived. The effect of flip angle and TR on image blurring was modeled using simulations and validated *in vivo*. A novel 2D-centric radial fan beam (RFB) k-space segmentation scheme was used to shorten scan times and improve parallel imaging. Healthy subjects as well as patients with multiple sclerosis and tremor were scanned using the optimized protocols.

Results—Inversion repetition times (TS) of 4.5s and 6s were found to yield the highest SNR efficiency for WMn MP-RAGE at 3T and 7T, respectively. Blurring was more sensitive to flip in WMn than in CSFn MP-RAGE and relatively insensitive to TR for both regimes. The 2D RFB scheme had 19% and 47% higher thalamic SNR and SNR efficiency than the 1D centric scheme for WMn MP-RAGE. Compared to 3T, SNR and SNR efficiency were higher for the 7T WMn regime by 56% and 41% respectively. MS lesions in the cortex and thalamus as well as thalamic subnuclei in tremor patients were clearly delineated using WMn MP-RAGE.

Conclusion—Optimization and new view ordering enabled MP-RAGE imaging with 0.8–1 mm³ isotropic spatial resolution in scan times of 5 minutes with whole brain coverage.

Keywords

Magnetization-prepared rapid gradient echo; MP-RAGE; 2D-centric k-space segmentation; radial fan beam segmentation; white-matter-nullled MP-RAGE

INTRODUCTION

Magnetization prepared rapid gradient echo (MP-RAGE), first introduced by Mugler et al. in 1990 [1], is routinely used for 3D T₁-weighted imaging, providing high spatial resolution isotropic whole brain imaging in short scan times with low specific absorption rate (SAR)

Address correspondence to: Manojkumar Saranathan, PhD Department of Radiology Lucas Center, MC 5488 Stanford University, Stanford CA 94305 manojksar@stanford.edu TEL: 650-724-7256.

penalty. The inversion time is usually set to null or significantly attenuate cerebrospinal fluid (CSF) signal, which results in good white matter (WM) - grey matter (GM) contrast. This sequence is routinely used in volumetric analysis, WM-GM segmentation, epilepsy imaging as well as in the detection and characterization of lesions from multiple sclerosis (MS) and other WM degenerative diseases [2–6]. We refer to this sequence, henceforth, as CSF-nulled (CSFn) MP-RAGE or conventional MP-RAGE. A variant of the MP-RAGE method was recently reported by Bluestein *et al* at 7T [5], where WM signal rather than CSF signal was nulled for better visualization of cortical MS lesions at 7T. We refer to this variant sequence as WM-nulled (WMn) MP-RAGE.

The analytical signal equation for MP-RAGE, first derived by Deichmann *et al.* [7], reveals a complex dependence on scan parameters such as inversion pulse repetition time (TS), number of readouts per inversion (N), excitation flip angle α , and the readout sequence repetition time (TR). Other parameters such as receiver bandwidth (BW) and RF pulse length also affect the signal, albeit indirectly. The optimal choice of scan parameters plays an important role in the signal-to-noise ratio (SNR), contrast, and blurring characteristics of MP-RAGE. Most of the studies reporting MP-RAGE have been at 3T, have used CSF nulling, and have converged to a “standardized” protocol that yields reasonably good SNR and excellent WM-GM contrast (the sequence parameters used in the Alzheimer's Disease Neuroimaging Initiative or ADNI study for instance [6]). However, for WMn MP-RAGE, the scan parameters have not yet been carefully optimized from a scan efficiency and blurring standpoint, to the best of our knowledge, especially at 7T. Bluestein *et al.* [5] who used the WMn MP-RAGE sequence at 7T for cortical MS lesion characterization, did not optimize scan parameters like TS and TR for SNR efficiency but rather used the shortest possible TS (3.7s) that achieved tolerable SAR. Tourdias *et al.* [8] further optimized the WMn MP-RAGE sequence for visualization of intra-thalamic nuclei at 7T, taking into account SNR and contrast efficiency, and reported an optimum TS of 6s, but did not consider the effect of other sequence parameters like N and BW. Visualization of the thalamus and the delineation of thalamic nuclei could be very useful in the diagnosis and management of brain pathologies such as tremor. In addition, the WMn MP-RAGE sequence could be useful for improved depiction of cortical and thalamic lesions in multiple sclerosis, if the scan time is shortened and SNR improved.

An important consideration in MP-RAGE is image blurring. Centric k-space ordering along one of the phase encoding directions (y or z) is preferred over sequential ordering in MP-RAGE when good contrast is desired, since the center of k-space is acquired closest to the inversion null point [9]. However, any significant modulation of signal close to the center of k-space results in image blurring as well as loss of contrast at the interface between different tissues, as shown by Deichmann *et al.* [7]. While Bluestein *et al.* [5] did not consider the effect of flip angle on blurring, Tourdias *et al.* [8] empirically studied the effect of α on image blurring and recommended the use of 4° excitation flip angles to minimize image blurring for WMn MP-RAGE at 7T. Due to the different signal recovery curves in CSFn and WMn MP-RAGE, the effect of blurring is expected to be different in the two MP-RAGE regimes but has not been well characterized hitherto.

Phase encoding order is another important consideration in MP-RAGE. While one-dimensional (1D) schemes such as sequential or centric along one of the phase encoding dimensions are commonly used, two-dimensional (2D) schemes have also been proposed based on square-spiral, elliptical-spiral or recessed elliptical centric phase ordering [10–12]. 2D k-space segmentation schemes can be efficient for many reasons- (a) they permit skipping the corners of k-space without loss of spatial resolution [13]; (b) they can help decouple N (the number of readout points acquired per IR pulse) from number of phase (N_y) or slice (N_z) encoding steps, making the scan prescription more flexible; and (c) they can enable 2D parallel imaging (along k_y and k_z), which can reduce g -factor noise by effectively distributing the parallel imaging acceleration across two directions. For all of these reasons, 2D segmentation schemes could be used to reduce the long scan times (16 min.) stemming from the increased TS (6s) at 7T recommended by [8], and would be valuable for many patient conditions (tremors or Parkinson's disease, for instance), where motion artifacts are often a concern. These schemes can also benefit conventional CSF_n MP-RAGE as the inversion preparation module is essentially decoupled from the acquisition module.

In this work, we started with the WM_n MP-RAGE sequence and further optimized the scan parameters for 7T as well as for 3T imaging. We modeled the effect of α and TR on image blurring and validated it using simulations and *in vivo* data. Using a novel radial fan beam 2D-centric k-space segmentation scheme, we demonstrated improved SNR efficiency as well as efficient 2D parallel imaging in clinically practical scan times for WM_n MP-RAGE. We then compared the performance of optimized WM_n MP-RAGE at 3T and 7T by scanning healthy human subjects, investigating the hypothesis that the use of low flip angles to reduce image blurring in WM_n MP-RAGE and the concomitant signal-to-noise ratio (SNR) reduction would favor ultra high field imaging despite the lengthened T_1 relaxation times. Lastly, we scanned patients with multiple sclerosis and tremors at 7T using the optimized MP-RAGE sequences to demonstrate their potential clinical utility.

METHODS

MP-RAGE optimization

Scan parameter optimization—Figure 1a shows the schematic of an MP-RAGE pulse sequence. The main parameters directly affecting signal are TS (or TD), N , and α . Receiver bandwidth BW affects the noise (and hence signal-to-noise SNR) but also changes TR, which in turn affects the signal. Assuming a fixed RF pulse width, we simply used BW instead of TR in the simulations, accounting for the lengthened TR caused by increased readout durations. The MP-RAGE signal equation as described by Deichmann et al. [7] was implemented in MATLAB. For the different species considered (WM, GM, CSF, lesions), T_1 , and proton density values at 3T and 7T gleaned (supplemental Table 1) from literature [14,15] were used in the modeling. SNR and CNR efficiency was computed by dividing the SNR by (scantime). Unlike the optimization of [8] that only considered the effect of TS, three sequence parameters – TS, N and BW – were simultaneously varied and the SNR efficiency globally optimized. Other empirical considerations included fat-water shift artifacts, which are more pronounced at lower receiver bandwidths, as well as an upper limit

on N which could increase blurring and reduce the uniformity of nulling, especially for small structures.

Image blurring—The degree of blurring at the interface between two tissues in MP-RAGE imaging is determined by the differential rate of modulation of the signal recovery curves of the two tissues, with higher differential modulation producing more blurring ([7], see also Appendix). The MP-RAGE signal recovery curve is in turn dependent on the apparent relaxation rate $1/T_1^*$ during the acquisition phase and is given by $(1/T_1 - \ln(\cos\alpha))/TR$. Hence, the effect of α and TR on contrast blurring was studied for both CSF and WM regimes by evaluating the differential point spread function (dPSF), which governs the signal spread at the boundary between two tissues. The dPSF, defined in the Appendix as the Fourier transform of the difference of simulated signal recovery curves for the two tissues of interest, is computed as a function of α and TR .

2D k-space segmentation—We employed a 2D-centric radial fan beam k-space segmentation scheme previously demonstrated for cardiac gated inversion-prepared 3D gradient echo imaging [16,17] (henceforth abbreviated as 2D RFB). An elliptical region inscribed inside a rectangular region of k_y - k_z was retained with the corners removed whilst sampling on a Cartesian grid, resulting in ~22% scan time reduction, without loss of spatial resolution along y or z (if zero filling is not used) as previously shown by Bernstein et al. [13]. Skipping the corners of k-space results in a theoretical SNR reduction by a factor of $(\pi/4) = 0.89$ compared to full k-space 1D centric acquisition. The elliptical region was then divided into M angular sectors with M given by $0.78*N_y*N_z/N$ where N is the number of k-space readouts (i.e. TRs) acquired per inversion, N_y and N_z the phase-encode and slice-encode resolution, and the 0.78 term added to account for the corner removal. The scan time for the 2D scheme is given by $M*TS = TS*0.78*N_y*N_z/N$ whereas for the 1D scheme, it is $TS*N_y$. Note that the use of additional acceleration in the z direction can help reduce scan time further in the 2D case (compared to acceleration along y or z alone) but not in the 1D case as scan time is independent of N_z for the 1D case. Within each radial fan beam, k-space was sorted in the order of increasing k_r , resulting in a readout train that originated in the center of k-space and fanned outward, in order to achieve high contrast, similar to other forms of centric encoding. The combination of the aforementioned k_r -based ordering as well as small fan angles minimizes jumps in k-space along each readout train and potential eddy current artifacts. The 2D RFB scheme is illustrated in Figure 1b.

Human imaging

All experiments were performed on GE Discovery MR750 3T and MR950 7T scanners (GE Healthcare, Waukesha, WI) with a 32-channel receive array head coil (Nova Medical, Wilmington, MA), which incorporated a birdcage transmit head coil in the case of 7T. All scans were conducted after obtaining prior informed consent compliant with our institutional review board (IRB). Ten healthy volunteers were scanned, starting with a 3-plane localizer and a higher-order shimming protocol, and then using a single 3D coronal slab covering the whole brain with each of the different MP-RAGE sequences. To investigate the effect of α on blurring, MP-RAGE scans were acquired on one healthy subject by varying α from 2° to 8° , in steps of 2° at 7T. To investigate the effect of k-space segmentation, 1D centric and 2D

RFB MP-RAGE, each acquired with optimized scan parameters, were compared on the 10 healthy subjects for both the CSF-nulled regime and the WM-nulled regime at 7T. To investigate the effect of field strength on WMn MP-RAGE, data from 10 healthy subjects scanned on both 3T and 7T MRI scanners on the same day were compared. Finally, to illustrate the potential clinical utility of this methodological development, we present data from a patient with multiple sclerosis (MS) and from a patient with tremor who were scanned at 7T with the optimized parameters derived from the above steps.

Scan parameters for the 7T WMn MP-RAGE sequence were- 180×180 matrix, 18 cm FOV, 1mm slice thickness, 200 slices, 10.1ms TR, 4.6 ms TE, 680 ms TI, ARC parallel imaging factor of 2.5×1 for 1D centric and 1.5×1.5 for 2D RFB. Scan parameters for the 7T CSFn MP-RAGE sequence were in accord with what has been reported in literature [4,18] 224×224 matrix, 18 cm FOV, 0.8mm slice thickness, 220 slices, 8.5ms TR, 3.9 ms TE, 3.7s TS, 1200 ms TI, ARC parallel imaging factor of 3×1 for 1D centric and 1.7×1.6 for 2D RFB. Scan parameters for the 3T WMn MP-RAGE sequence were identical to those of 7T except for TI, TS and α where the optimal values for the respective field strength were used (see Table 1). A whole volume excitation pulse (nonselective hard pulse) was used for whole brain coverage in the coronal plane, which also yielded the shortest possible TR, other things like BW being fixed. For homogeneous inversion, we used an optimized 16 ms generalized hyperbolic secant (HSn) pulse whose amplitude modulation function is given by $\text{sech}(\beta\tau^n)$, as reported in [19], with $n = 1.25$ and $\beta = 4.5$ for all the MP-RAGE imaging experiments. SAR was monitored in all cases using the vendor supplied SAR monitor on the scanner and was below 0.5 W/kg for all scans

Image analysis

For the blurring experiment, we used signal profiles across clearly identifiable structures in the axial reformatted plane to characterize blur. For the WMn regime, the signal profile along an oblique line passing through the anterior arm of the internal capsule (where the WM fibers are embedded between the GM of the lenticular nucleus on one side and the caudate nucleus on the other side) was plotted. For the CSFn regime, signal profile along an oblique line passing through a dilated perivascular space where a CSF filled structure is embedded within WM was plotted. In both conditions, we reasoned that WM (for WMn regime) or CSF (for CSFn regime) should be nulled and that any blur would smooth the profile by mixing in signal from the surrounding tissue.

To study the influence of k-space segmentation and of field strength, SNR and SNR efficiency were computed and compared for all the sequences. For the 7T CSFn MP-RAGE data, CNR and CNR efficiency for WM-GM contrast were also computed. For the WMn regime, an ROI inside the thalamus was used for SNR measurements whereas for the CSFn regime, ROIs placed within cortical grey matter and adjoining white matter were used for SNR calculations. A Student's t-test was used to determine statistical significance with p-values < 0.05 deemed as statistically significant.

RESULTS

MP-RAGE parameter optimization

Figure 2 shows MATLAB simulation results of the effect of TS, N and BW simultaneously on SNR efficiency for the WMn regime at 3T (top) and 7T (bottom). At lower TS values where there is insufficient time for relaxation at the end of the readout, increasing N beyond a point decreases SNR efficiency. As TS increases, this effect reverses and higher N always leads to higher SNR efficiency. Note that lowering the BW yields higher SNR efficiency at all values of TS, presumably from the SNR gain at lower BWs that outweighs the loss from decreased recovery time. From the curves, it can be seen that TS=5s, N=320, and BW=12kHz for 3T and TS=7s, N=320, and BW=12kHz are optimal for 7T. For *in vivo* scans, we restricted maximum value of N to 240 so as to not compromise the quality of inversion, especially for small structures. The optimal values that were actually used for the scans for the different cases, incorporating this limit on N, are summarized in Table 1 and indicated by black arrows in Figure 2.

MP-RAGE image blurring

Differential PSF (dPSF) computed as the Fourier transform of the difference in the MP-RAGE signal recovery curves (GM–WM for WMn, WM–CSF for CSFn) are shown in Figure 3. The flip angle α was varied from 3° to 12° in steps of 3° (bottom row) and TR varied from 6 to 12 ms in steps of 2 ms (top row) for the CSFn regime (left column) and the WMn regime (right column). It can be seen that the effect of TR on dPSF (and by extension blurring) is minimal for both regimes. It can also be clearly seen that α affects the dPSF curves more substantially, especially in the tails of the distributions, and more for the WMn regime than for the CSFn regime. These observations imply some restrictions on the maximum α that can be used in the WMn regime, in line with the low α value recommended by [8] based on empirical optimization.

Axial reformatted sections of coronally acquired volumes obtained in a human volunteer at 7T for α values of 2°, 4°, 6° and 8° for the WMn regime (top row) and CSFn regime (middle row) are shown in Figure 4. The bottom left panel shows line profiles drawn across the anterior arm of the internal capsule (dotted line box in a, inset in c) representing a WM-GM edge for the different flip angles for the WMn regime. The bottom right panel shows line profiles drawn across a small CSF “hole” in WM (dotted line box in b, inset in d) representing a CSF-WM edge for the different flip angles for the CSFn regime. It can be seen both visually on the images and on the line profiles that the extent of blurring is much higher at the higher flip angle range for the WMn case than for the CSFn case, agreeing with the differential PSF based predictions. Taking into account an increased B_1 of a factor of 1.5 in the thalamus at 7T (measured using a Bloch-Siegert B_1^+ mapping sequence, data omitted for clarity), the flip angles use correspond to that of the simulations shown in Figure 3.

2D k-space segmentation

The use of 2D-centric segmentation with cut corners enabled a scan time reduction of a factor of 1.5× (1.28 from the skipped corners of k-space as well as a factor of 1.2 from using a higher N=240 compared to $N_z=200$). For the WMn and CSFn regime, 2D ARC parallel

imaging factors of 1.5×1.5 and 1.7×1.6 respectively (roughly corresponding to 1D acceleration factors of 2.5 and 3) were used for the 2D RFB scheme resulting in a scan times of 5.2 min and 4 min. For the 1D centric scheme, 1D ARC parallel imaging factors of 2.5 and 3 resulted in scan times of 8 min and 5.2 min for the WMn and CSFn regimes respectively.

Table 2 compares the SNR and SNR efficiency of the two regimes for the 1D and 2D cases (mean and SD across 10 healthy subjects). It can be seen that for the WMn regime, the thalamic SNR and SNR efficiency are both higher for the 2D RFB compared to the 1D centric scheme by 19% and 47% respectively ($p < 0.05$). For the CSFn regime, the SNR efficiency was higher for the 2D RFB scheme than for the 1D scheme by 24% ($p < 0.05$) while the SNR was not significantly different. The increased efficiency allows us to achieve 1mm isotropic whole-brain resolution in under 5 min scan times, even for WMn which requires higher TS and lower alpha than traditionally used for MP-RAGE. The scan times for the CSFn MP-RAGE were on the order of 4 minutes with 0.8 mm isotropic spatial resolution.

A comparison of coronal sections acquired using the 1D centric and 2D RFB WMn-MP-RAGE sequence from a human volunteer at 7T is shown in Figure 5 (top panel). The 2D RFB image has visibly higher SNR with negligible increase in blurring. CSFn-MP-RAGE images acquired using the 1D centric and 2D RFB scheme in the same volunteer is shown in the bottom panel. Note the reduction in parallel imaging artifacts (arrows) achieved due to the distribution of the parallel imaging reduction (and concomitant reduction in g-factors) as well as the increased SNR of the 2D sequence. Yellow boxes show the ROIs used for SNR calculations in both regimes.

3T vs. 7T comparisons

At 3T, the highest flip angle that yielded acceptable blurring was 6° determined from empirical measurements over a range of flip angles. Note that this roughly matches the 4° flip angle at 7T, accounting for an increased B_1 heterogeneity of $\sim 1.5X$ in the center of the brain at 7T. Figure 6 shows a comparison of 3T vs. 7T WMn MP-RAGE images obtained on the same volunteer. The SNR improvements at 7T are evident. The mean thalamic SNR and SNR efficiency were 56% and 41% higher ($p < 0.05$) at 7T compared to 3T for the 10 subjects scanned at both field strengths (last row of Table 2).

Imaging of MS and tremor patients at 7T

Coronal WMn (left) and CSFn (right) MP-RAGE sections acquired from a patient with MS at 7T are shown in Figure 7. Both WM (thin arrows) and cortical grey matter lesions (thick arrows, top insets) can be clearly visualized in the WMn as well as the CSFn regime images. The bottom panel shows a section containing the thalamus with an axial reformat shown in the inset. It can be seen that the lesions in the thalamus (orange arrows) are clearly highlighted only in the WMn regime but not on the CSFn regime, underscoring the utility of WMn MP-RAGE in visualization of the thalamus and thalamic lesions. Figure 8 shows coronal sections (left column) from a patient with suspected essential tremor obtained using the WMn MP-RAGE (a) and CSFn MP-RAGE (b) with the area inside the dashed white

rectangles zoomed and shown in the middle column. There are two lesions (arrows), compatible with old strokes, one within the ventral posterior lateral (VPL) nucleus and a smaller one within the lateral posterior (LP) nucleus depicted with stars on the histological plate based on the Morel atlas[20] (bottom right) to illustrate the location of these lesions. The strokes, which are the likely explanation for the patient's tremor and dystonia, were not visible on 1.5T or 3T or 7T T_2 weighted imaging but were clearly visualized using the WMn MP-RAGE sequence. They were also not visualized in the CSFn MP-RAGE sequence. The top right panel shows the segmentation of a few of the subnuclei superimposed on the WMn MP-RAGE section, illustrating again the utility of the WMn regime in depiction of the thalamic subnuclei as previously demonstrated [8] but now with substantially shorter scan times (~5min vs. ~16min).

DISCUSSION AND CONCLUSIONS

We have demonstrated an optimized WMn MP-RAGE sequence capable of achieving 1 mm³ isotropic spatial resolution with whole brain coverage in about 5 minutes at both 3T and 7T. This sequence could be very useful for delineating thalamic lesions and subnuclei [8] as well as WM and cortical lesions in multiple sclerosis. For the WMn regime, the use of a 2D centric radial fan beam k-space segmentation improved thalamic SNR and SNR efficiency by 19% and 47% compared to the conventional 1D centric sequence at 7T. This 2D RFB scheme was also used with conventional CSFn MP-RAGE at 7T, where it improved SNR efficiency by 24% and allowed whole brain coverage with 0.8 mm isotropic spatial resolution in 4 minutes. The SNR efficiency gain from 2D RFB scheme is higher for WMn MP-RAGE than for CSFn MP-RAGE, presumably due to the poorer g-factors for the deep brain structures near the center of the coil, where the thalamic SNR was measured.

Blurring seems to show a higher sensitivity to α in the WMn regime than in the CSFn regime. In CSFn MP-RAGE, the inversion times are long (1.5s typically) and there is significant recovery of the signal for tissues such as GM and WM by time the center of k-space is acquired, resulting in reduced modulation of k-space and reduced blurring. However, for WMn MP-RAGE, the inversion times are much shorter (650ms typically) and the signal is more strongly modulated for WM and GM, when the center of k-space is acquired, resulting in higher sensitivity to blurring. For both CSFn and WMn regimes, the differential PSF as function of α has a central peak that is largely invariant to α and the effects of α seem to occur almost entirely in the “tails” of the dPSF distributions, which are clearly non-Gaussian. This characteristic of the α effect leads to more of a “smearing” than a traditional “blurring”. This effect can be clearly seen in Fig 4a where the internal capsule (a white matter filled region inside a GM zone) can be clearly seen as increasingly “smeared” out as the flip angle is increased from 2° to 8° for the WMn regime. This can also be seen in the profiles (Fig 4c) reflected as a “filling” of the well. The effect is lesser for CSFn than for WMn as predicted by the simulations.

The thalamic SNR was higher for 7T WMn 2D RFB vs. 7T WMn 1D centric despite the reduction in the amount of k-space acquired due to skipping of the k-space corners, presumably due to the improved g-factors from the use of 2D parallel imaging especially in the center of the brain, where the thalamus is located. The use of 2D parallel imaging helped

distribute the artifacts more equitably in both directions. This can be seen in the CSFn imaging example of Figure 5 where a 1D parallel imaging factor of 3 resulted in residual ghosting that is significantly attenuated in the 2D case. While 2D parallel imaging can also be applied to the conventional 1D centric k-space scheme, there is no scan time advantage as the scan time is proportional to $TS \cdot N_y$ and acceleration along the z-direction does not affect scan times unlike the 2D RFB case.

Unlike conventional CSFn MP-RAGE, the optimal flip angle for 7T WMn MP-RAGE is 4° which makes it SNR limiting while the optimal TS is 6s, which increases the scan time. By using the 2D RFB scheme, we were able to limit the scan time to 5 minutes, which is clinically viable from the point of view of motion sensitivity. This is a significant reduction in scan time from the 16 minute scan times proposed in [8], while still retaining the ability to perform segmentation of the thalamic nuclei. In contrast, the optimal values of flip angle and TS are 7° and 4.5s, respectively, for 3T WMn MP-RAGE. The use of lower flip angle and higher TS, as well as increased T_1 values at 7T, all act to dampen the SNR and SNR efficiency increases at 7T compared to 3T; despite this, we achieved a 56% increase in SNR and 41% increase in SNR efficiency at 7T compared to 3T for WMn MP-RAGE. Previous efforts at optimization of image contrast in MP-RAGE have either been at 3T using GM-nulling [14,15] for cortical contrast or have been partial, taking only TS into account [8]. We have optimized the WMn MP-RAGE sequence for optimal SNR and contrast for visualization of the thalamic nuclei and lesions at 7T.

While we sought to optimize N, BW and TS for maximizing the SNR efficiency in WMn MP-RAGE, we had to constrain the upper limit of N based on inversion efficiency considerations. The centric k-space traversal scheme implies that the outer parts of k-space are acquired farther and farther away after inversion, resulting in T_1 recovery of the high k-space frequencies. This would manifest as imperfect inversion, especially at the edges of small objects. The BW was also constrained at the lower end to be 12 kHz based on fat-water pixel shift considerations, which is increased at 7T (1000 Hz fat-water shift). This was empirically determined from scans performed on a range of BW. The use of chemical fat suppression could enable the use of lower BWs and improve SNR even further but would suffer from the vulnerability of fat suppression to B0 and B1 heterogeneity effects. Nevertheless, the parameters used TS (6s), BW (12 kHz) and N (240) are significantly different from what is commonly used for conventional MP RAGE imaging. We focused on the WMn regime in this work but the same parameter optimization can also be applied to conventional CSFn MP-RAGE, where there are two conflicting parameters (SNR and contrast) that need to be considered.

Future work would incorporate prospective motion correction schemes that would further improve motion robustness, especially in patients with uncontrollable tremors. The use of motion compensation could enable the elimination of parallel imaging, which is currently used to shorten the long acquisition times. This could be especially beneficial at 3T to improve SNR and achieve image quality comparable to that of 7T. This work employed a 2D-centric radial fan beam segmentation scheme which imparts a modest amount of motion robustness due to the dispersed nature of the point spread function as demonstrated in [21]. A systematic comparison of the relative merits and demerits of different 2D-centric

trajectories like radial fanbeam, square spiral and recessed elliptical centric would be useful but is beyond the scope of this work.

The use of automated strategies to segment the thalamic nuclei is currently under investigation to study the effect of WMn SNR and contrast on the ability to visualize the subnuclei. This visualization could be very useful in neurosurgical applications like implantation of deep brain stimulation (DBS) electrodes and targeting for thalamic ablation, which require precise localization of the subnuclei. The visualization of thalamic subnuclei on a patient specific basis could improve targeting accuracy compared to atlas based registration schemes currently employed. We have shown preliminary data to illustrate the ability of the WMn regime to delineate the subnuclei and also identify lesions in the thalamus, not clearly visualized using the conventional CSFn MP-RAGE sequence or T₂ weighted sequences.

In conclusion, a 2D-centric radial fan beam segmented white-matter nulled MP-RAGE sequence was optimized for SNR efficiency and used to acquire 1 mm³ isotropic brain images on healthy volunteers and patients with multiple sclerosis and tremor in under 5 minutes. The same k-space segmentation scheme was used to acquire conventional CSF nulled MP-RAGE with 0.8 mm³ isotropic spatial resolution in 4 minutes. We have also shown definitive advantages (in terms of improved SNR and SNR efficiency) of 7T vs. 3T for delineation of the sub-structures within the thalamus.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to thank Karla Epperson, Ann Sawyer, and Dr. May Han for their help with subject and patient data acquisition. This work was supported by NIH P41 EB015891-19, Richard M. Lucas Foundation and GE Healthcare. T. Tourdias received financial support from ARSEP Foundation (Fondation pour l'aide à la recherche sur la Sclérose en Plaques); CHU de Bordeaux, Fondation Université de Bordeaux and Translational Research and Advanced Imaging Laboratory (TRAIL) program – France; Institut Servier; and France-Stanford Center for Interdisciplinary studies.

APPENDIX

Consider a synthetic line phantom consisting of a line of species A with one pixel of species B embedded in the middle. Let the proton density of the two species be ρ_A and ρ_B respectively. Without loss of generality, we can assume that species B is at the origin (center) of the line and write the object as

$$\rho_A (1 - \delta(x)) + \rho_B \delta(x)$$

which is equivalent to $\rho_A \delta(k) - \rho_A + \rho_B$ in k-space after a 1D Fourier transform.

If we assume that the MP-RAGE modulation functions for A and B are $s_A(k)$ and $s_B(k)$, then k-space gets modulated and can be written as $s_A(k) (\rho_A \delta(k) - \rho_A) + s_B(k) \rho_B$ which after Fourier transforming to image domain becomes

$$\rho_A s_A(0) + \rho_B FT \{s_B(k)\} - \rho_A FT \{s_A(k)\}$$

If we assume $\rho_B \sim \rho_A = \rho$, this reduces to

$$\rho s_A(0) + \rho \cdot FT \{s_B(k) - s_A(k)\}$$

The first term is just a constant while the second term is the differential modulation of A and B i.e. the differential PSF (dPSF), which causes the edge smearing. If there is no differential modulation and $(s_B - s_A)$ a constant function, then the object can be fully recovered (scaled by ρ , the proton density of the object).

REFERENCES

1. Mugler JP 3rd, Brookeman JR. Three-dimensional magnetization-prepared rapid gradient-echo imaging (3D MP RAGE). *Magn Reson Med.* 1990; 15:152–157. [PubMed: 2374495]
2. Filippi M, Mastronardo G, Rocca MA, Pereira C, Comi G. Quantitative volumetric analysis of brain magnetic resonance imaging from patients with multiple sclerosis. *J Neurol Sci.* 1998; 158:148–153. [PubMed: 9702685]
3. Hulsey KM, Gupta M, King KS, Peshock RM, Whitemore AR, McColl RW. Automated quantification of white matter disease extent at 3 T: comparison with volumetric readings. *J Magn Reson Imaging.* 2012; 36:305–311. [PubMed: 22517404]
4. Tallantyre EC, Morgan PS, Dixon JE, Al-Radaideh A, Brookes MJ, Morris PG, Evangelou N. 3 Tesla and 7 Tesla MRI of multiple sclerosis cortical lesions. *J Magn Reson Imaging.* 2010; 32:971–977. [PubMed: 20882628]
5. Bluestein KT, Pitt D, Sammet S, Zachariah CR, Nagaraj U, Knopp MV, Schmalbrock P. Detecting cortical lesions in multiple sclerosis at 7 T using white matter signal attenuation. *Magn Reson Imaging.* 2012; 30:907–915. [PubMed: 22578928]
6. Jack CR Jr, Bernstein MA, Fox NC, et al. The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI methods. *J Magn Reson Imaging.* 2008; 27:685–691. [PubMed: 18302232]
7. Deichmann R, Good CD, Josephs O, Ashburner J, Turner R. Optimization of 3-D MP-RAGE sequences for structural brain imaging. *Neuroimage.* 2000; 12:112–127. [PubMed: 10875908]
8. Tourdias T, Saranathan M, Levesque IR, Su J, Rutt BK. Visualization of intra-thalamic nuclei with optimized white-matter-nulled MPRAGE at 7T. *Neuroimage.* 2014; 84:534–545. [PubMed: 24018302]
9. Holsinger AE, Riederer SJ. The importance of phase-encoding order in ultra-short TR snapshot MR imaging. *Magn Reson Med.* 1990; 16:481–488. [PubMed: 2077339]
10. Stocker T, Shah NJ. MP-SAGE: A new MP-RAGE sequence with enhanced SNR and CNR for brain imaging utilizing square-spiral phase encoding and variable flip angles. *Magn Reson Med.* 2006; 56:824–834. [PubMed: 16947341]
11. Conklin J, Winter JD, Thompson RT, Gelman N. High-contrast 3D neonatal brain imaging with combined T1- and T2-weighted MP-RAGE. *Magn Reson Med.* 2008; 59:1190–1196. [PubMed: 18429019]
12. Lin C, Bernstein MA. 3D magnetization prepared elliptical centric fast gradient echo imaging. *Magn Reson Med.* 2008; 59:434–439. [PubMed: 18183604]
13. Bernstein MA, Fain SB, Riederer SJ. Effect of windowing and zero-filled reconstruction of MRI data on spatial resolution and acquisition strategy. *J Magn Reson Imaging.* 2001; 14:270–280. [PubMed: 11536404]
14. Bock NA, Hashim E, Janik R, Konyer NB, Weiss M, Stanis GJ, Turner R, Geyer S. Optimizing T1-weighted imaging of cortical myelin content at 3.0 T. *Neuroimage.* 2013; 65:1–12. [PubMed: 23036446]

15. Rooney WD, Johnson G, Li X, Cohen ER, Kim SG, Ugurbil K, Springer CS Jr. Magnetic field and tissue dependencies of human brain longitudinal $^1\text{H}_2\text{O}$ relaxation in vivo. *Magn Reson Med*. 2007; 57:308–318. [PubMed: 17260370]
16. Saranathan M, Glockner J. Three-dimensional dixon fat-water separated rapid breathheld imaging of myocardial infarction. *J Magn Reson Imaging*. 2013; 38:1362–1368. [PubMed: 23559381]
17. Bayram E, Michelich CR, Vu AT, Busse RF. Adaptive Centric View Ordering for Magnetization Prepared Gradient Echo Imaging. *Proc ISMRM, Toronto*. 2008; 16:3508.
18. van der Kolk AG, Hendrikse J, Zwanenburg JJ, Visser F, Luijten PR. Clinical applications of 7 T MRI in the brain. *Eur J Radiol*. 2013; 82:708–718. [PubMed: 21937178]
19. Tannus A, Garwood M. Adiabatic pulses. *NMR Biomed*. 1997; 10:423–434. [PubMed: 9542739]
20. Morel A, Magnin M, Jeanmonod D. Multiarchitectonic and stereotactic atlas of the human thalamus. *J Comp Neurol*. 1997; 387:588–630. [PubMed: 9373015]
21. Saranathan M, Bayram E, Madhuranthakam A. Azimuthal Sorting in Tandem with Elliptical Reordering (ASTER): A New K-Space Reordering scheme for Reduced Motion Sensitivity. *Proc ISMRM, Honolulu*. 2009; 17:4605.

Figure 1.

(a) Schematic of the MP-RAGE sequence (b) the radial fan beam k-space segmentation scheme- within each fan beam, points are sorted in increasing radial distance from the center and traversing smoothly outward.

Figure 2. Thalamic SNR efficiency (% , normalized to maximum) as a function of TS, bandwidth and N for the WM-nulled MP-RAGE sequence at 3T (a) and 7T (b). Arrows indicate the parameters used for the optimal protocols.

Figure 3.

Differential point spread functions (dPSF) plotted for different values of TR (top row) and flip angle α (bottom row) for the CSF-nulled (left column) and WM-nulled (right column) MP-RAGE sequences at 7T. The dPSF was computed as the Fourier transform of WM–GM or WM–CSF signal difference for WMn and CSFn respectively. Note that the dPSF is sensitive to α for the WMn regime and insensitive to TR in both regimes. TS values of 6s and 3.7s were used for WMn and CSFn, respectively.

Figure 4.

WM-nulled (a) and CSF-nulled (b) images obtained at flip angles of 2°, 4°, 6° and 8° from a healthy subject at 7T to study the effect of blurring on the two regimes. The insets show the structures used to compute the edge profiles to evaluate the blurring for both regimes. The higher sensitivity of the WM-nulled sequence to flip angle can be seen from the “shallowing” of the profiles for $\alpha > 4^\circ$ compared to the CSF-nulled sequence (c vs. d).

Figure 5.

Comparison of 1D centric vs. 2D radial fan beam (RFB) for the WMn regime (a, b) and the CSFn regime (c, d). The use of 2D parallel imaging helps improve overall image quality in the 2D RFB segmentation scheme as seen in the zoomed insets of the thalamus for the WMn regime and reduced residual ghosting in the CSFn regime. Yellow boxes show the locations of the ROIs used for SNR calculations for cortical GM, WM and thalamic structures.

Figure 6.

Comparison of WMn MP-RAGE at 3T (left) and 7T (right), each using the optimal TS and flip angles (Table 2) for the respective field strengths and the remaining parameters held constant. The inset zooms show an axial reformat of the thalamus region showing the increased SNR at 7T, especially of the thalamic nuclei.

Figure 7.

Coronal WMn (left column) and CSFn MP-RAGE (right column) sections from a multiple sclerosis patient with the cortical (thick white arrows), WM (thin arrows) and thalamic lesions (orange arrows) illustrated. Two different slice locations are shown in the top and bottom rows. The insets in the bottom row show the thalamus in a reformatted axial plane. While WM and cortical lesions can be seen on both regimes, the thalamic lesion is clearly visualized only in the WMn MP-RAGE regime.

Figure 8.

Coronal sections (left most column) from a patient with suspected essential tremor obtained using the WMn MP-RAGE (a) and CSFn MP-RAGE (b) sequences. The middle column shows inset zooms of the thalamus region. Two lesions (arrows), compatible with old strokes, one within the VPL nucleus and a smaller one within the LP nucleus (depicted using stars on the Morel atlas plate, bottom right) can be seen in the WMn sequence but not in the CSFn sequence or T₂ weighted sequences (not shown). Manual segmentation of some of the thalamic nuclei superimposed on the WMn image is also shown for reference (top right).

Table 1

WMn MP-RAGE sequence parameters

	WMn 7T	WMn 3T
TS (ms)	6000	4500
α (deg)	4	7
N	240 [*]	240 [*]
BW	+/- 12 kHz [†]	+/- 12 kHz [†]
TI (ms)	680	500
Scan time (min)	5.2	4.0

^{*} upper limit constrained by inversion efficiency[†] lower limit constrained by fat-water artifacts

Table 2

Image analysis results: SNR and SNR efficiency

	SNR	SNR _{eff}
7T WMn 2D RFB	17.9±5.1 ^{*,#}	7.8±2.2 ^{*,#}
7T WMn 1D centric	15.0±4.5	5.3±1.6
7T CSFn 2D RFB	21.4±4.9	10.8±2.5 [*]
7T CSFn 1D centric	19.7±4.5	8.7±2.0
3T WMn 2D RFB	11.4±1.9	5.5±0.9

^{*} 2D RFB vs. 1D centric at 7T,

[#] 2D RFB 7T vs. 2D RFB 3T