Published in final edited form as:

Magn Reson Med. 2020 November ; 84(5): 2400–2411. doi:10.1002/mrm.28283.

Three Dimensional Motion Corrected T1 Relaxometry with MPnRAGE

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Abstract

Purpose: To test the performance of the MPnRAGE motion correction algorithm on quantitative relaxometry estimates.

Methods: Twelve children (9.4+/-2.6 years, min=6.5 years, max = 13.8 years) were imaged three times in a session without sedation. Stabilization padding was not used for the second and third scans. Quantitative T1 values were estimated in each voxel on images reconstructed with and without motion correction. Mean T1 values were assessed in various regions determined from automated segmentation algorithms. Statistical tests were performed on mean values and the coefficient of variation across the measurements. Accuracy of T1 estimates were determined by scanning the High Precision Devices (HPD) MRI System phantom with the same protocol.

Results: T1 values obtained with MPnRAGE agreed within 4% of the reference values of the HPD phantom. The best fit line was $T1(\text{MPnRAGE}) = 1.02 T1(\text{reference}) - 0.9 \text{ ms}$, $R^2=0.9999$. For in vivo studies, motion correction reduced the coefficients of variation of mean T1 values in whole brain tissue regions determined by FSL FAST by 74+/-7%, subcortical regions determined by FIRST and FreeSurfer by 32+/-21% and 33+/-26% respectively. Across all participants, the mean coefficients of variations ranged from 0.8 to 2.0% for subcortical regions and 0.6+/-0.5% for cortical regions when motion correction was applied.

Conclusions: MPnRAGE demonstrated highly accurate values in phantom measurements. When combined with retrospective motion correction, MPnRAGE demonstrated highly reproducible T1 values, even in participants who moved during the acquisition.

Keywords

Motion correction; Relaxometry; T1; R1; MPnRAGE

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Introduction

Quantitative relaxometry imaging methods have been used to investigate changes in brain tissues ranging from development^{1–7}, aging, myelination and pathology. The general approach common to all methods is the collection of a series of images with different acquisition parameters, i.e. flip angles, repetition times (TRs), inversion times (TIs), etc. in order to estimate the underlying parameters. This may also include additional “calibration” scans to measure scanner imperfections such as scans to map the magnetic field inhomogeneity (B0 map) or radio-frequency transmit field (B1map). Head motion, both during individual scans or between the different scans poses a challenge to robust parameter estimation. To date, almost all of the effort in reducing the effects of motion in quantitative relaxometry have been in registration of the individual source images. This works well when the individual images are not corrupted by motion artifacts and the relative motion between scans is minimal. However, spatial interpolations used in this step can produce unwanted smoothing effects and inaccuracies⁸. Larger motions between the individual scans may be problematic for high density receiver arrays with rapidly varying spatial sensitivities since the signal at each anatomical location is then modulated with a different coil sensitivity in each of the images. Since the receiver sensitivity is typically incorporated into an effective “spin density”, this effectively creates an additional unknown parameter with each new motion event. The gross effects can largely be reduced using intensity correction methods^{9,10}, but subtle effects are likely to persist. Motion during the scans results in corrupt images, such as the ghosting artifacts when Cartesian k-space sampling is used or image blurring when radial k-space sampling is used¹¹. One strategy for dealing with motion is to acquire redundant data, i.e. more than the minimum number of flip angles, TIs, etc. required to perform fitting in anticipation of rejecting motion corrupted images during a quality control step of the processing; however, this increases the minimum scan time and decreases the measurement efficiency.

Quantitative relaxometry, especially quantitative T1 in children is a highly desirable method to track normal and abnormal brain development as myelin content is believed to be a major factor contributing to T1¹². However, accurate and stable methods needed to track such changes are difficult to achieve in children as motion effects are more dominant than in adults. Although sedation may be used to reduce motion, it is generally not feasible in research studies and many clinical centers are trying to minimize the use for clinical studies due to potential side effects.¹³ In studies of very young children, imaging during natural sleep has been used as a strategy for minimizing motion^{14,15}; however, motion can still occur and the strategy becomes less effective for older children. Prospective motion correction using optical tracking, imaging navigators, and FID navigators are also promising strategies^{16,17}, but remain largely unvalidated at correcting motion in quantitative relaxometry¹⁸. Retrospective motion correction methods have recently been developed for low resolution 2D T1 and T2 relaxometry mapping with MR fingerprinting¹⁹. To date, there are few demonstrations of motion corrected relaxometry with 3D, high resolution, whole brain methods.¹⁸

Retrospective motion correction using self-navigation with k-space blades (i.e., PROPELLER^{–20}) or 3D radial k-space sampling are also promising strategies for motion

correction.²¹ Recently, an inversion-prepared 3D radial imaging sequence, MPnRAGE, was proposed as a novel technique for simultaneously generating multiple inversion-recovery contrasts and quantitative T1 imaging²². Subsequently, the reconstruction for this pulse sequence was adapted to enable retrospective motion correction using low resolution images reconstructed from the measurements following each inversion recovery pulse²³. MPnRAGE motion correction has been demonstrated to generate consistently high quality whole-brain T1-weighted images in a neuroimaging study of children with autism and typical development²³. More recently, high test-retest performance of automated segmentations was demonstrated on a cohort of unsedated pediatric children imaged with motion corrected MPnRAGE.²⁴ Since retrospective motion correction with MPnRAGE was shown to consistently provide high quality T1-weighted images, we hypothesized that these methods would also enable improved quality and consistency of quantitative T1 relaxometry from the same data. In this study, retrospective motion-corrected T1 relaxometry with MPnRAGE was evaluated in a test-retest study of twelve children scanned without sedation.

Methods

Study Population

Imaging experiments were performed with institutional review board approval and informed consent/assent. Twelve children (9.4 $\pm$ 2.6 years, min=6.5 years, max=13.8 years, 6 male and 6 female) without known neurological health concerns were selected for imaging. Recruitment was not based on likelihood of subjects remaining still during the scan.

Image Acquisition

All exams took place on a 3T MRI scanner (Discovery MR750, GE Healthcare, Waukesha, WI) without the use of sedation. Participants watched a video of their choice and were instructed to remain still. The participants heads were stabilized within a 32 channel head coil (Nova Medical, Wilmington, MA) using the NoMoCo pillow support system (NoMoCo Pillow, Inc., La Jolla, Ca). After receiving a single MPnRAGE acquisition and prospectively corrected T1-weighted MPRAGE acquisition (6-7 minutes), some of the padding was removed to allow further range of motion. Each subject then received two additional MPnRAGE and MPRAGE acquisitions in alternating order. The order of all scans was counter-balanced across subjects. The prospectively corrected MPRAGE acquisitions were not used in this analysis as they did not provide T1 estimates.

MPnRAGE Background—A magnetization (inversion) prepared rapid gradient echo (i.e. MPRAGE²⁵) sequence was modified to collect a large number, n , gradient echoes (i.e. MPnRAGE²³) with a 3D radial k-space trajectory after each preparation pulse. The trajectory ordering was quasi-randomly ordered to approximately distribute projection angles uniformly within each gradient echo block as well as across each gradient echo block, at each inversion time. Low resolution navigator images are formed using data within each gradient echo block to estimate motion parameters. Motion correction is performed directly in k-space using the Fourier Shift Theorem to correct translations and by rotating the k-space trajectories to correct for rotations. Thus, errors from spatial interpolations are eliminated. Differently contrasted images (i.e. inversion time images) are formed using the

collection of data at a specific inversion time, but across all gradient echo blocks and are used to estimate T1 by fitting to a known model, derived by solving the Bloch equations.

MPnRAGE Acquisition Parameters: Whole brain coverage with 1.0 mm isotropic resolution was acquired in the axial orientation with 200 slices. Parameters included, TR=4.9 ms, TE=1.8 ms, $n=386$ views along the recovery curve. The excitation flip angles were $4^\circ/8^\circ$ for the first 325/remaining 61 views. A delay time of $T_D=500$ ms occurred after the last TR of each gradient echo block to allow the signal to recover before the next preparation pulse. The scan time was 7 minutes.

MPnRAGE Reconstruction and T1 Fitting Procedure: Composite T1-weighted images using the entire k-space dataset for each scan were reconstructed both with and without motion correction. Complex valued source images corresponding to each of the 386 inversion times (12ms to 1889ms, evenly spaced by 1TR) were reconstructed with and without the motion correction algorithm described in²³ by summing the individual coil images according to²⁶. A two pass fitting procedure similar to²⁷ was performed that initially fit all voxels for 4 unknowns (T1, spin density, B1, and inversion efficiency) using a known model determined by solving the Bloch equations. The B1 and inversion efficiency maps were smoothed using a 3D-Gaussian kernel with full-width half-max at 7 and 9 mm, respectively. The T1 and spin density maps were then refit while fixing the model using the smoothed B1 and inversion efficiency maps. The T1 maps from the second fitting pass were then denoised using total variation (TV) minimization.

Phantom Scans: The High Precision Devices (HPD) system phantom (Model 130) was used to assess the accuracy of estimated T1 values from MPnRAGE. The HPD system phantom developed by a joint effort between the National Institute of Standards and Technology (NIST) and the International Society for Magnetic Resonance in Medicine (ISMRM), contains 14 spherical samples with a range of known T1 values²⁸. All image acquisition, reconstruction, and fitting procedures were the same as the in-vivo experiments. Mean T1-values of each phantom were compared to the known values using linear regression.

ROI selection & T1 measurement: The T1-weighted composite images for each subject were used as inputs to *fsL_anat* from the FMRIB Software Library v5.0 and *recon-all* from FreeSurfer. “*fsL_anat*” is a wrapper provided in the FMRIB Software Library that performs biasfield correction, brain and lesion extraction, whole brain white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF) segmentations with FAST²⁹ (a hidden Markov random field model), and subcortical segmentations with FIRST³⁰ (a Bayesian approach of shape and appearance). In addition, the *recon-all* tool from FreeSurfer generated a cortical surface based segmentation³¹ and subcortical segmentation with a Bayesian approach using a realistic image likelihood term as well as a prior model³². The default settings were used for both programs, although the images were initially corrected for the strong receiver biases using *N4BiasFieldCorrection*, part of the ANTS software package and described in⁹, before calling *recon-all*. For analysis, the whole brain white matter (WM), gray matter (GM) and cerebrospinal fluid (CSF) masks from the FAST segmentations of *fsL_anat*, as well as the

subcortical masks for the thalamus-proper, caudate, putamen, pallidum, hippocampus, amygdala, accumbens-area from both hemispheres and the brain-stem/4th ventricle were obtained from FIRST and FreeSurfer automated segmentations.

Since the quantitative T1 maps are inherently aligned with the T1-weighted composite images, no additional registration steps are needed for alignment with the segmentation masks other than to correct for some 90 degree rotations introduced by each method needed for rough alignment with their prior images, which may be corrected for with FSL's *fslreorient2std* and FreeSurfer's *mri_convert* utilities. The T1 values of all voxels within each region for each scan and subject are saved and used for analysis. Values within the cortical surface determined by FreeSurfer are sampled at the midpoint between the white matter / gray matter boundary and the pial surface using FreeSurfer's tool *mri_vol2surf* with option "--projfrac 0.5".

Prior Analyses—The T1-weighted composite images were previously analyzed in ²⁴, which demonstrated high test-retest of the automated segmentation algorithms used throughout this study.

Analyses—For region of interest (ROI) based analyses, the stability of the mean T1 value within each ROI across repeated measurements within a subject is assessed using the coefficient of variation (COV). The mean and standard deviations of the COV across all subjects was computed for each ROI. Statistical differences in the mean and standard deviation of the COVs with and without correction were assessed using paired-sample t-tests and two-sampled F-tests. a Bonferroni multiple comparison correction was used to adjust the significance level to $p=0.05/m$, where m is the number of measurements for each method.

Results

The results from the HPC phantom scan are shown in Table 1. Across a wide range of values, encompassing those expected in the human brain (T1 values between about 2000ms and 350ms), MPnRAGE differed from the reference values less than 4%. The best fit line was $T1(\text{MPnRAGE}) = 1.02 T1(\text{reference}) - 0.9 \text{ ms}$, $R^2=0.9999$ using phantoms T1-1 through T1-13. T1 estimation for phantom T1-14, with $T1 \sim 28\text{ms}$, was off by about 7 ms (23%).

Example T1 weighted images and T1 maps and estimated motion parameters are shown in Figures 1–3 for subjects demonstrating negligible/minor (Fig 1), moderate (Fig 2), and severe (Fig 3) motion artifacts. Supporting Information Videos S1 and S2 contain six examples in animated GIF format illustrating the differences in T1-weighted and quantitative T1 maps with and without motion correction for cases with mild, moderate, and severe motion artifacts. Figure 1 demonstrates the ability to improve even minor motion artifacts that are hardly noticeable on the uncorrected images. Moderate motions in Figure 2 are nearly eliminated after motion correction, while artifacts from severe motions in Fig. 3 are considerably reduced, but not necessarily entirely eliminated.

The results of T1 reliability for whole brain WM, GM, and CSF segmentations from FAST are shown in Figure 4 and Supporting Information Table S1. All three tissue types had statistically significant differences in the mean between the motion corrected and non motion corrected T1 values, but only CSF had a statistically significant difference of the standard deviation. With motion correction, the mean and standard deviations of the COVs for all regions were significantly reduced ($P<0.05/3$), with motion correction offering a profound decrease in the COV (1.3% vs 7.5% for CSF, 0.5% vs 1.9% for GM and 0.7% vs 2.4% WM). Compared to the values without motion correction, the COVs with motion correction are on average 74%/–7% less. Bland-Altman plots of the T1 value differences with and without corrections are presented in Figure 5 (color coded by region of interest) and Supporting Information Figure S1 (color coded by subject) for all measurements of all subjects. Most of the measurements with and without correction were relatively consistent although larger differences were observed across multiple regions and cases.

The results from the FSL FIRST and FreeSurfer segmentations are presented in Figures 6–8 and Supporting Information Tables S2–S5. Seven of fifteen regions in FIRST and seven of fifteen regions in FreeSurfer had significantly different T1 values when measured with and without motion correction after corrections for multiple comparisons ($P<0.05/15$). With motion correction, the average COV was reduced for all regions except the right thalamus. The mean values of the regional COVs after motion correction were between 0.8–2.0%. Compared to the values without motion correction, the COVs after motion correction are lower on average 32%+/-21% and 33%+/-25% for FSL FIRST and FreeSurfer, respectively. The reduction in COV was judged statistically significant for at least one segmentation method for all regions except the left and right amygdala and palladium. However, only the left hippocampus were significant at the multiple-comparisons correction level of $P<0.05/15$. Bland-Altman plots of the T1 values with and without are presented in Figure 8 (color coded by region of interest) and Supporting Information Figures S2–S3 (color coded by subject) for all measurements of all subjects. The mean T1 values increased after motion correction by about 1% for each method, although both methods had about one third (32% and 35% or FIRST and FreeSurfer) of the cases report decreases.

Mean cortical T1 values are increased from 1539 ms $\pm$ 80 ms without motion correction to 1615 ms $\pm$ 40 ms with motion correction. A paired sample t-test confirms that this shift is significant ($p=0.004$) and a f-test confirms that the standard deviations are statistically different ($p=0.03$). When averaged across all subjects, the COV of mean cortical T1 was 4% $\pm$ 4% without motion correction and 0.6% $\pm$ 0.5% with motion correction.

Discussion

This study demonstrated that MPnRAGE yields highly accurate and reliable quantitative T1 mapping. The quantitative T1 mapping with MPnRAGE was found to be remarkably consistent with the gold standard NIST calibrated T1 phantom²⁸. Similar results were observed with in vivo comparisons between MPnRAGE T1 mapping and a 2D inversion recovery quantitative T1 mapping method²⁷. Even when child participants were not sedated and did not have their head well stabilized within the head coil, MPnRAGE demonstrated high reproducible T1 values within automatically labeled regions. When motion correction

was applied, not only was the COV reduced in almost all regions, but the T1 values also showed small, albeit statistical differences illustrating the importance of motion correction.

Retrospective motion correction was found to be highly effective for improving the reliability of quantitative T1 mapping in young children. We note that motion-corrected MPnRAGE was 100% successful in providing images for automated brain segmentation without major failure. While the study did not investigate specific types or scripted motion, the method appeared to be highly robust to a broad range of motion amplitudes and types (sharp transitions, jittery, and slow variations). This study was performed in children as young as 6 years of age without head restraints so it is anticipated that the reliability will be even better for more compliant cohorts with padding to help minimize head motion. A limitation is that the small sample size is not sufficient to fully characterize the performance as a function of the motion behavior.

The low COV of T1 with motion-corrected MPnRAGE, even in this challenging cohort, indicates that MPnRAGE will be an outstanding tool for quantitative brain imaging studies. Lower variability in T1 estimation will improve statistical power of statistical detection of small brain changes, particularly for within-subject longitudinal studies. A prior work¹⁸ used a prospective motion correction approach with a motion camera and Moire phase marker to demonstrate reduced coefficients of variation in 3D, high resolution quantitative R1 relaxometry and magnetization transfer (MT). That approach offered a considerable reduction in median COVs, however, the resulting median COV for R1 with motion correction was still high ($\sim 15\%$) and had pronounced artifacts in the motion corrected R1 maps. Since the no motion case had median COV about 13%, it is not clear if the large COV was due to motion, or perhaps an aggressive protocol consisting of 0.8 mm isotropic resolution that would suffer from inherently lower SNR than a 1.0 mm protocol. A separate study used the same relaxometry method without motion correction in a cohort of adult control subjects and found the COVs to be about 4 to 5 percent when 1.0 mm isotropic spatial resolution was used³³. In another study of quantitative T1 relaxometry of adult control subjects (23.2 $\pm$ 3.6yrs) without motion correction and with 1.2 mm isotropic resolution, the mean intrasubject COVs was reported at less than 1%³⁴. In contrast, this manuscript reported COVs of 1–2% for 1mm T1 relaxometry from pediatric participants scanned without stabilization pads.

Although statistical differences between T1 maps with and without motion correction exist in most regions, one somewhat surprising finding in this work was the relative similarities of the quantitative T1 values. This is likely due to the inherent insensitivities of radial k-space trajectories to motion, which tend to produce a slight blurring artifact as opposed to the traditional ghost artifact with Cartesian k-space trajectories¹¹. Since the T1 and proton density values within a tissue region are expected to be highly homogenous, and since other parameters like B1 and inversion efficiency are expected to slowly vary across space, the parameter fitting is likely most affected near regional boundaries. Thus, voxels near regional boundaries may produce inaccurate parameter estimates when motion is not corrected. Reduced resolution may also hinder automated segmentation methods, causing inaccurate segmentations. We should also note that although FIRST and FreeSurfer are widely used on pediatric populations there has not been extensive validation or comparison with manual

segmentations. One recent manuscript reported lower agreement between automatically segmented regions from FIRST and FreeSurfer to manually segmented regions of hippocampus and amygdala volumes from pediatric participants, although the authors could not exclude motion artifacts from contributing to the quality of the automated segmentations³⁵. Without performing manual segmentations, it is difficult to determine if the observed statistical changes in T1 without motion correction are due to tissue signal mixing, inaccurate boundaries/segmentations, or a combination of the two.

Conclusions

MPnRAGE demonstrated highly accurate quantitative T1 relaxometry as assessed with HPD System phantom. A test-retest study of 12 pediatric participants scanned without sedation and stabilization pads was used to demonstrate highly reproducible T1 values, as assessed with region of interest measurements determined from automated segmentation techniques. Statistical differences were observed between T1 values obtained with and without motion correction, suggesting the importance of motion correction when performing quantitative relaxometry.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:
T1-weighted images and quantitative T1 maps from a 79 month old boy demonstrating ability of MPnRAGE to correct for subtle motion artifacts.

Figure 2:
T1-weighted images and quantitative T1 maps from a 108 month old boy demonstrating ability of MPnRAGE to correct for moderate motion artifacts.

Figure 3:
T1-weighted images and quantitative T1 maps from a 92 month old female demonstrating ability of MPnRAGE to correct for severe motion artifacts arising from nearly continuous motion events throughout the duration of the scan.

Figure 4:

T1 values (top) and coefficients of variation (bottom) from regional measurements in whole brain white cerebrospinal fluid, gray matter, and white matter segmentations from FSL FAST across all subjects. Superscripts ^{t,f} denote $p < 0.05$ for t-tests and f-tests, used to test for statistical differences of the means (t-tests) and standard deviations (f-tests) between the motion corrected and non-motion corrected T1 values. The T1 values for CSF have been multiplied by 0.5 to preserve dynamic range of the plots.

Figure 5:

A comparison of the quantitative T1 values measured in automatically segmented regions of interest using FAST. Shown are all measurements from all subjects and trials, color coded by region of interest. The y-axis shows the difference of T1 values after motion correction, normalized by the mean value, indicating an average increase of T1 after motion correction was applied. The black dashed line is the mean of the normalized difference, while the thin red lines are at ± 1.96 standard deviations from the mean.

Figure 6:

T1 values (top) and coefficients of variation (bottom) from regional measurements in subcortical segmentations from FSL FIRST across all subjects. Superscripts ^{t,f} denote $p < 0.05$ for t-tests and f-tests, used to test for statistical differences of the means (t-tests) and standard deviations (f-tests) between the motion corrected and non-motion corrected T1 values.

Figure 7:
T1 values (top) and coefficients of variation (bottom) from regional measurements in subcortical segmentations from FreeSurfer across all subjects. Superscripts ^{t,f} denote $p < 0.05$ for t-tests and f-tests, used to test for statistical differences of the means (t-tests) and standard deviations (f-tests) between the motion corrected and non-motion corrected T1 values.

Figure 8:

A comparison of the quantitative T1 values measured in automatically segmented regions of interest using FIRST and FREESURFER. Shown are all measurements from all subjects and trials, color coded by region of interest. The y-axis shows the difference of T1 values after motion correction, normalized by the mean value, indicating an average increase of T1 after motion correction was applied. The black dashed line is the mean of the normalized difference, while the thin red lines are at ± 1.96 standard deviations from the mean.

Table 1:

Estimated T1 values from the HPC System Phantom. Excluding phantom T1-14, the best fit line was $T1(\text{MPnRAGE}) = 1.02 T1(\text{reference}) - 0.9 \text{ ms}$, $R^2=0.9999$

Sample Name	Reference (ms)	MPnRAGE (ms)	MPnRAGE (% error)
T1-1	1989 ± 1.0	2021 ± 270	1.6 %
T1-2	1454 ± 2.5	1497 ± 130	3.0 %
T1-3	984.1 ± 0.33	1005 ± 54	2.1%
T1-4	706 ± 1.5	730 ± 33	3.4%
T1-5	496.7 ± 0.41	506 ± 28	1.9%
T1-6	351.5 ± 0.91	351 ± 21	-0.3%
T1-7	247.13 ± 0.086	256 ± 12	3.4%
T1-8	175.3 ± 0.11	172 ± 7	-2.21%
T1-9	125.9 ± 0.33	129 ± 6	2.3 %
T1-10	89.0 ± 0.17	92 ± 5	2.8 %
T1-11	62.7 ± 0.13	63 ± 6	0.8 %
T1-12	44.53 ± 0.090	42 ± 6	-5.1 %
T1-13	30.84 ± 0.016	30 ± 7	-1.7 %
T1-14	27.719 ± 0.0054	21 ± 6	-23%