Published in final edited form as:

NMR Biomed. 2016 April ; 29(4): 411–419.

Impact of uncertainty in longitudinal T_1 measurements on quantification of dynamic contrast-enhanced MRI

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Abstract

The objective of this study was to assess the uncertainty in T_1 measurement, by estimating the repeatability coefficient (RC) from two repeated scans, in normal appearing brain tissues employing two different T_1 mapping methods. All brain MRI scans were performed on a 3 T MR scanner in 10 patients who had low grade/benign tumors and partial brain radiation therapy (RT) without chemotherapy, at pre-RT, 3 weeks into RT, end RT (6 weeks) and 11, 33, and 85 weeks after RT. T_1 -weighted images were acquired using (1) a spoiled gradient echo sequence with two flip angles (2FA: 5° and 15°) and (2) a progressive saturation recovery sequence (pSR) with five different TR values (100–2000 ms). Manually drawn volumes of interest (VOIs) included left and right normal putamen and thalamus in gray matter, and frontal and parietal white matter, which were distant from tumors and received a total of accumulated radiation doses less than 5 Gy at 3 weeks. No significant changes or even trends in mean T_1 from pre-RT to 3 weeks into RT in these VOIs ($p = 0.11$, Wilcoxon sign test) allowed us to calculate the repeatability statistics of between-subject means of squares, within-subject means of squares, F -score, and RC. The 2FA method produced RCs in the range of (9.7–11.7)% in gray matter and (12.2–14.5)% in white matter; while the pSR method led to RCs ranging from 10.9 to 17.9% in gray matter and 7.5 to 10.3% in white matter. The overall mean ($\pm$ SD) RCs produced by the two methods, 12.0 ($\pm$ 1.6)% for 2FA and 12.0 ($\pm$ 3.8)% for pSR, were not significantly different ($p = 0.97$). A similar repeatability in T_1 measurement produced by the time efficient 2FA method compared with the time consuming pSR method demonstrates that the 2FA method is desirable to integrate into dynamic contrast-enhanced MRI for rapid acquisition.

Keywords

T_1 measurement; uncertainty in T_1 ; repeatability coefficient; DCE-MRI; brain tissues

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INTRODUCTION

A fast, accurate, and precise measurement of longitudinal relaxation time (T_1) is crucial for diagnosis, prognosis, and monitoring therapeutic response in a variety of diseases either by comparing the native T_1 values in longitudinal studies or by quantifying the physiological parameters in dynamic contrast-enhanced (DCE) MRI (1). In the DCE data quantification, to convert the DCE signal intensity to the contrast concentration–time curve, native T_1 is a critical parameter (2). Because the native longitudinal relaxation rate ($R_{10} = 1/T_{10}$) is like a scaling factor to the signal intensity change before and after contrast injection, any error in the R_{10} measurement propagates into the DCE-MRI-derived kinetic parameters proportionally (3,4). Therefore, it is crucial to minimize the impact of the uncertainty in T_1 measurement on DCE quantification to improve its statistical power in clinical application.

There are a large number of T_1 mapping methods utilizing different MR pulse sequences and acquisition parameters (5). However, a wide range of measured T_1 values for the same tissue and field strength has been reported, which raises a major concern over accuracy and precision in T_1 measurement (6). To date, only a few studies have examined the uncertainty in T_1 measurement using test–retest data (7–10). An early study that measured T_1 values in a single subject brain five times using an inversion recovery (IR) sequence on a 1.5 T scanner reported coefficients of variation (CoVs) of T_1 in nine different tissue regions (7). A recent study including four healthy volunteers measured brain T_1 twice during the same imaging session using a slice-shifted multi-slice IR echo planar imaging sequence on a 7 T scanner, and reported average ratios of the mean difference to mean T_1 value between two measurements in seven different tissue regions (8). A recent cardiac study compared the uncertainty of four myocardial T_1 mapping methods (two modified Look–Locker (LL) and two saturation recovery (SR) sequences) in seven healthy human subjects, and reported the absolute difference of mean T_1 values across subjects between two repeated scans (9). Finally, a study examined the repeatability of T_1 measurement in osteoarthritis-prone knee joints in nine subjects employing the IR, LL and dual-flip-angle (2FA) methods, and reported the root means of squares of CoV for the three methods (10). Although all these studies used quantitative metrics to characterize the uncertainty in T_1 measurement, it is difficult to generalize these findings due to the differences in study designs, pulse sequences, tissue of interest, statistical methods, and metrics for characterization of T_1 uncertainty. For example, T_1 measurement uncertainty assessed in healthy subjects during the same imaging session could be very different from that in patients with repeated scans done over a period of weeks or even months. Different pulse sequences can also have different repeatability behaviors. Different metrics for characterizing T_1 measurement uncertainty make comparison and interpretation of the data difficult. Recently, through collaborative efforts (e.g. Quantitative Imaging Biomarkers Alliance (QIBA) and NCI Quantitative Imaging Network), guidelines have been published for assessment of repeatability of quantitative image measurements, including statistical analysis and metrics (11).

The objective of this study was to assess the uncertainty in T_1 measurement in normal appearing brain tissues of patients with brain tumors by estimating the repeatability coefficient (RC) from two repeated scans following the recently recommended guidelines (11). A previous study, examining the radiation-induced effect by measuring T_1 changes in

33 pediatric patients, has reported that radiation doses lower than 20 Gy cause no radiation-induced injury in normal white matter, and even higher doses have no effect on gray matter (12). Considering that the pediatric patients at the development stage are more sensitive to the radiation-induced effect than adult patients, the dose limit having no effect on pediatric patients is likely applicable to adult patients. In agreement with this assumption, a prospective study performed in our laboratory to investigate the radiation dose effect on normal brain vasculature in 10 adult patients using DCE-MRI-derived parameters showed that tissue regions receiving 0–20 Gy had non-significant changes in blood plasma volume (v_p) and transfer constant (K^{trans}) (13). Since these DCE-MRI parameters are derived from a series of DCE T_1 -weighted images, the dose limit causes no change in these parameters and therefore can equally be applied to the corresponding T_1 measurements. Thus, the present study analyzed the T_1 variations in volumes of interest (VOIs) in frontal and parietal white matter and deep gray matter of the putamen and thalamus, which received accumulated doses less than 5 Gy in the middle (10 Gy at the end) of radiation therapy (RT). Two commonly used T_1 mapping methods, 2FA and progressive saturation recovery (pSR) with five different repetition times (TR), were used to acquire the two repeated scans over a period of three weeks. The individual T_1 changes in longitudinal studies, up to 85 weeks, were also evaluated to examine whether the changes were within the uncertainty range defined by the estimated RC. The impact of the uncertainty of T_1 measurement on quantification of physiological parameters from DCE-MRI is discussed.

MATERIALS AND METHODS

Human subjects

Ten patients (four male, six female; age range, 26–59 years; mean age, 46 ± 9 years) participating in a prospective, institutional review board approved, longitudinal DCE-MRI study that aimed to investigate radiation dose effect on normal brain vasculature were included in this study. These patients had low grade brain tumor or benign tumor and received partial brain RT. None of these patients received chemotherapy during 85-week follow-ups or had tumor recurrence. They had MRI scans pre-RT, in the middle of 6-week RT, at the end of RT, and 1, 6, and 18 months post-RT (0, 3, 6, 11, 33, and 85 weeks after starting RT). Manually drawn VOIs included the normal appearing frontal and parietal white matter and deep gray matter of the putamen and thalamus, which were distant from tumor and received a total of accumulated radiation doses less than 5 Gy in the middle (3 weeks) of RT. Since the normal tissue VOIs in these patients received doses less than 5 Gy in the middle of RT, and such a low dose does not cause any radiation-induced effect on measured T_1 (12,13), we considered using the T_1 data acquired at 0 weeks and 3 weeks as test and retest data to estimate RCs in T_1 measurements. In order to do so, we further tested whether there were any significant T_1 changes in the VOIs between 0 weeks and 3 weeks using a paired t test and Wilcoxon signed test, and compared between-subject means of squares (BMSs) to within-subject means of squares (WMSs) using F statistical analysis (F -score = BMS/WMS). The T_1 values measured at later time points were evaluated to see whether the mean T_1 values were significantly different from pre-RT T_1 values using a Wilcoxon sign test, and the percentage changes in longitudinal T_1 measurements were compared to see whether they were within the uncertainty ranges defined by the estimated RCs.

MR acquisition parameters

T_1 acquisition—All brain MRI scans were performed on a 3 T MR system with a 16 channel receiver coil (Achieva, Philips). T_1 -weighted images were acquired using (1) a 3D spoiled gradient echo sequence with two flip angles (2FA) (5° and 15°) and (2) a 3D pSR sequence with five different TR values (100, 200, 500, 1000, and 2000 ms). Both methods acquired images with a matrix of $128 \times 128 \times 80$ and a voxel size of $2 \times 2 \times 2 \text{ mm}^3$. The 2FA acquisition used TE/TR = 2.8/7.6ms and total acquisition time 2 min; while the pSR had TE = 1.1ms and 6min acquisition time with parallel imaging factors of 2 in anterior to posterior direction and in right to left direction. Other MRI scans included the high resolution pre- and post-contrast T_1 -weighted images (matrix size $256 \times 256 \times 160$, voxel size $0.94 \times 0.94 \times 1$, TE/TR = 4.6/9.7ms), T_2 -weighted fluid-attenuated inversion recovery (FLAIR) images (matrix size $352 \times 352 \times 30$, voxel size $0.68 \times 0.68 \times 5$, TE/TR/TI = 125/11000/2800 ms) and DCE T_1 -weighted images.

T_1 quantification— T_1 maps were quantified from two image sets acquired by the 2FA method, and five image sets from the pSR method, by nonlinear least-square fitting the data to the following signal intensity (S) equation:

$$S = M_0 \frac{(1 - \exp(-TR/T_1)) \sin\theta}{(1 - \exp(-TR/T_1) \cos\theta)} \quad [1]$$

where M_0 represents the equilibrium longitudinal magnetization, using an in-house functional image analysis tool (FIAT) software package (14). Image intensities were appropriately scaled prior to analysis (15). As these studies were part of an old large group study, neither the B_1 field nor the flip angle correction was performed for T_1 measurements. After generating the quantitative T_1 maps, they were co-registered with post-contrast T_1 -weighted images at 0 weeks using rigid body transformation (14). VOIs were manually drawn on the registered T_1 maps (Fig. 1). The VOI size was 142.4 mm^3 (81 voxels) for all patients. In order to examine the VOI size effect on the estimated RCs, we reduced the VOI size by a factor of nine from the original size of 142.4 mm^3 to 15.8 mm^3 (from 81 to 9 voxels). Then, a mean T_1 value in each VOI of each patient was calculated.

Estimates of repeatability coefficient

To calculate the RC of T_1 , a one-way analysis of variance model was used (16). Let X_{ik} represent the observed value of mean T_1 in a VOI for the i th subject ($i = 1, 2, \dots, n$) at the k th replication ($k = 1, 2$), then

$$X_{ik} = \mu_i + \varepsilon_{ik} \quad [2]$$

where μ_i is the true value and ε_{ik} represents the measurement error.

If there is no significant difference of the observed values of mean T_1 between two repeated tests, and the difference does not depend on the combined mean, the relative BMS and WMS are estimated from

$$\text{BMS} = \frac{2}{n} \sum_{i=1}^n \left(\frac{\hat{X}_i - \hat{X}}{\hat{X}} \right)^2 \quad [3]$$

and

$$\text{WMS} = \frac{1}{n(2-1)} \sum_{i=1}^n \sum_{k=1}^2 \left(\frac{X_{ik} - \hat{X}_i}{\hat{X}_i} \right)^2 = \frac{1}{n} \sum_{i=1}^n \frac{1}{2} \left(\frac{X_{ir} - X_{it}}{\hat{X}_i} \right)^2 \quad [4]$$

where X_{it} , X_{ir} , and $\hat{X}_i$ denote the test, retest, and average value over replications for the i th subject, respectively, and $\hat{X}$ is the grand mean of overall observations from all subjects. Between-subject standard deviation (bSD) and within-subject standard deviation (wSD) are calculated from $\text{bSD} = \sqrt{(\text{BMS} - \text{WMS})/2}$ and $\text{wSD} = \sqrt{\text{WMS}}$, respectively. The relative RC is estimated from $\text{RC} = 1.96 \sqrt{2\text{wSD}^2} = 2.77 \sqrt{\text{WMS}}$. Therefore, 95% of the subjects are expected to have a difference between two repeated measurements between $-\text{RC}$ and RC .

Since WMS is distributed as $\chi_{n(K-1)}^2 \text{wSD}^2 / n(K-1)$, the 95% confidence interval of the estimated RC is given by (16)

$$\text{RC}_L = 2.77 \sqrt{\frac{n(K-1)\text{WMS}}{\chi_{n(K-1)}^2(0.975)}} = \text{RC} \sqrt{\frac{n(K-1)}{\chi_{n(K-1)}^2(0.975)}} \quad [5a]$$

$$\text{RC}_U = 2.77 \sqrt{\frac{n(K-1)\text{WMS}}{\chi_{n(K-1)}^2(0.025)}} = \text{RC} \sqrt{\frac{n(K-1)}{\chi_{n(K-1)}^2(0.025)}} \quad [5b]$$

where $\chi_{n(K-1)}^2(a)$ is the a th percentile of the chi-square distribution with $n(K-1)$ degrees of freedom and $K=2$. The upper and lower bounds of RC can be used as a conservative estimate of RC.

In order to examine whether the within-subject variance of the repeated measurements was statistically significant compared with the between-subject variance, an F -test statistic was employed. F -score was calculated as the ratio of the BMS to the WMS.

RESULTS

Comparison of T_1 values between the first two tests

First, we tested if radiation doses of 5 Gy or less could cause any significant or even marginally significant T_1 changes in normal tissue at 3 weeks compared with 0 weeks. The T_1 values at 0 weeks were not significantly different from ones at 3 weeks in any VOI for both acquisition methods (p values ranged from 0.99 to 0.11 by Wilcoxon signed rank test) (Table 1), suggesting that radiation doses of 5 Gy or less did not cause any significant effect on T_1 values of normal tissue at 3 weeks. The T_1 standard deviations (SDs) across the patients produced by the pSR method, with ranges of 273–327 ms and 117–259 ms in gray matter and white matter, respectively, were observed to be higher than those of the 2FA approach: 47–141 ms and 44–134 ms in respective regions. However, when examining the voxel-wise T_1 variation in each patient, the pSR method produced small mean T_1 SD in the range of 44–98 ms and 26–46 ms in gray matter and white matter regions, respectively, compared with the 2FA-produced mean T_1 SD: 63–128 ms and 38–53 ms in respective regions.

Before estimating RCs, we compared the BMS with the WMS of T_1 values by using F statistical analysis. The 2FA method produced BMSs of $(2.04\text{--}8.33) \times 10^{-3}$ in gray matter and $(1.03\text{--}5.22) \times 10^{-2}$ in white matter, which were significantly greater than the WMSs of $(1.22\text{--}1.79) \times 10^{-3}$ in gray matter and $(1.94\text{--}2.41) \times 10^{-3}$ in white matter in all VOIs except three by F statistical analysis; see Table 1. The lowest F -score of 1.7 ($p \approx 0.24$) was observed in right putamen, whereas in left putamen and thalamus it was 2.7 ($p = 0.13$) and 3.6 ($p \approx 0.08$), respectively, which were not statistically significant. Similarly, the pSR method led to BMSs of $(7.62\text{--}10.25) \times 10^{-2}$ in gray matter and $(3.60\text{--}15.98) \times 10^{-2}$ in white matter, which were significantly greater than the WMSs in all VOIs: $(1.58\text{--}4.20) \times 10^{-3}$ and $(7.38\text{--}14.0) \times 10^{-4}$ in respective gray matter and white matter regions; see Table 1. Such significantly large BMSs compared with WMSs indicate that the T_1 variation is dominated by between-subject variation instead of within-subject variation. Therefore, it is reasonable to use the first and second T_1 measurements as test and retest data to estimate the RC.

Further, when examining the magnitude and direction of the relationship between absolute difference in mean T_1 values between test and retest and their combined means, the difference was not significantly dependent on the combined mean in any VOIs (p values range from 0.07 to 0.99: Kendall tau test) except one (right thalamus with the pSR method), for which a significant negative correlation was found ($p = 0.04$), indicating that the T_1 measurement error was independent of the magnitude of the measured T_1 values.

Repeatability coefficient estimates

Since there was no significant or even a trend in difference in measured T_1 values between 0 weeks and 3 weeks, the within-subject variation was significantly smaller than the between-subject variation, and the differences in mean T_1 values between two measurements were not dependent upon their combined means, the relative RC of T_1 measurements was estimated for each VOI using the data obtained at 0 weeks and 3 weeks for each of the two acquisition methods (Table 2).

In the large VOIs, the 2FA method produced RCs in the range of 9.7–11.7% in gray matter and 12.2–14.5% in white matter; while the pSR method led to RCs ranging from 10.9–17.9% in gray matter and 7.5–10.3% in white matter (Table 2). The overall mean ($\pm$ SD) RCs produced by the two methods, 12.0 ($\pm$ 1.6)% and 12.0 ($\pm$ 3.8)% for 2FA and pSR methods, respectively, were not significantly different (paired t test, $P = 0.97$).

VOI size effect on estimated RCs

We examined the VOI size effect on the estimated RCs by reducing the VOI size by a factor of nine (Table 2). When comparing small VOIs to large ones, RCs increased by a factor of 1.4 at most for the 2FA method, and 1.2 for the pSR method, for which both factors are much smaller than nine (the volume ratio of two VOIs), indicating that image noise is not the dominant factor affecting the RC.

Longitudinal percentage changes in T_1

Variations of T_1 measurements at later time points were evaluated and compared with the uncertainty range defined by the estimated RC interval ($-RC$, RC) in each VOI and for each acquisition method. Only 3 out of 64 studies ($8 \text{ VOIs} \times 4 \text{ time points} \times 2 \text{ methods}$) showed a weak significant differences in T_1 (p value range, 0.02–0.05; Wilcoxon sign test), indicating that there is little late radiation effect on measured T_1 values at this dose level. The longitudinal percentage changes in T_1 for each VOI of each patient at 6, 11, 33, and 85 weeks are plotted in Figures 2, 3 for 2FA and pSR methods, respectively. Considering all VOIs and time point studies, the 2FA method produced 89% and 83% of individual T_1 changes within the estimated RC interval for gray matter and white matter VOIs respectively, while the corresponding value for the pSR method were 85% and 82% in gray and white matter respectively. Specifically, 27%, 7%, 5%, and 31% of the longitudinal T_1 changes by the 2FA method were beyond the RC intervals at 6, 11, 33, and 85 weeks respectively, while 19%, 13%, 14%, and 36% of T_1 changes by the pSR method were beyond the uncertainty range in the respective time intervals.

DISCUSSION

In this study, we have evaluated the repeatability in T_1 measurements of normal appearing brain tissues, using 2FA and pSR methods, and the repeatability metrics proposed by QIBA (11). The overall RCs are 10.8% and 13.2% by the 2FA method and 14.9% and 9.1% by the pSR method for respective gray matter and white matter regions. The impact of such large variations of T_1 measurement cannot be neglected while quantifying the DCE-MRI. Most interestingly, the repeatability of T_1 measurements by the time-efficient 2FA method is similar to that of the time-consuming pSA method with five TR values. Since the DCE-MRI requires a rapid and precise measurement of pre-contrast T_1 , the multiple-flip-angle method, if optimized, is desirable to integrate in the DCE-MRI brain protocol for quantification of physiological parameters.

In recent years, a number of studies have evaluated the feasibility of DCE-MRI-derived kinetic parameters, such as plasma volume (v_p), volume transfer constant (K^{trans}) etc., in diagnosis, monitoring therapeutic response, and prediction of overall clinical outcomes in

several tumor types, reporting a decrease in K^{trans} and v_p due to therapeutic effect (17,18). However, the uncertainty in repeated T_1 measurements can reduce the repeatability of the parameters derived from DCE-MRI, and affect the statistical power of the parameters in clinical application. The present study shows that the variation in repeated T_1 is up to 15% in the VOIs of brain tissue if measured a few weeks apart, which presents an interval of repeated measures performed in typical clinical studies. Considering the proportional relationship of R_1 before and after contrast injection to native R_{10} as $(S/S_0)R_{10}$, where S is the T_1 -weighted signal intensity change before and after contrast injection and S_0 is the baseline signal intensity before contrast injection, the 15% error in native T_1 is directly propagated into R_1 as $15\% (S/S_0)/T_{10}$ even though there is no repeatability error in (S/S_0) . Thus, minimizing the T_1 variation could provide a more stable estimate of DCE-MRI parameters.

The increase in clinical utility of T_1 measurement motivates development of T_1 mapping methods that have time efficiency and better accuracy and precision (5). The conventional T_1 mapping methods, such as IR and SR, although providing a more accurate and precise T_1 measurement, are too slow to be used in clinical settings (19). The variable-flip-angle method employing a spoiled gradient echo sequence provides time efficiency and a better signal–noise ratio (SNR) in T_1 measurement (20), but suffers from the transmitted B_1 field inhomogeneity. Considering the sources of error, a number of studies have refined this method to optimize T_1 measurements with reasonable accuracy and precision by B_1 field and/or flip angle correction (21,22). To minimize the scan time, two flip angles have been suggested (23). However, considering the range of T_1 values in tissues of interest, it is hard to provide the best precision measurements for all T_1 values with a single pair of flip angles (20). Though the selection of optimal flip angles mainly depends on the range of T_1 values in the tissues to be measured, it also depends on selected TE and TR values. Selection of optimal flip angles, based on least-square solution for T_1 from the respective signal intensity equation, can be made to provide the precise T_1 measurements (24). This has been carried out in a phantom study.

In this study, we made a one-to-one comparison on precision between two T_1 mapping methods: 2FA with 5° and 15° flip angles and pSR with five different TR values (100–2000 ms), by evaluating the repeatability in T_1 values in brain tissue measured a few weeks apart. The mean T_1 values in normal brain tissues measured by both methods agreed well with previously reported values for 3 T MR systems (6). There are some limitations to comparing the T_1 repeatability measured herein with the previously reported results, as different organ tissues, repeatability matrices, and acquisition methods were used to characterize the T_1 uncertainty. However, the estimated T_1 repeatability in the present study is in close agreement to the previously reported result, a T_1 uncertainty range of 9.3–15.2% measured as the root mean square CoV in osteoarthritis-prone knee joints by the 2FA (4.8° and 23.9°) method (10). When comparing the T_1 repeatability estimated herein between the two methods, the 2FA method produced a more stable T_1 measurement in gray matter (small RC values) compared with white matter; while the pSR method produced lower RC values in white matter. This could be in part due to the fact that the two flip angles that we used were more optimal for the longer T_1 in gray matter than white matter (23). Overall comparison of the estimated RCs between the two methods shows that the pSR method produces a wide

range of RCs compared with the 2FA method. Since there are pros and cons to each method, and the accuracy and precision depend on clinical requirements, the present study suggests that the variable flip angle method, even with two flip angles and without B_1 field correction, is not inferior in T_1 mapping of brain tissues compared with the pSR method, and definitely has an advantage on scanning time, which is beneficial for a DCE-MRI protocol. Combining multiple flip angles with rapid B_1 field correction, the variable-flip-angle method can be optimized to provide an efficient method for T_1 mapping with adequate accuracy and precision. While T_1 accuracy was not addressed in the present study, bias that exists in 2FA can be corrected (6).

Several factors can affect the accuracy of the estimated RC in this study, including SNR, image registration, patient repositioning, partial volume effect, sample size, B_1 field inhomogeneity, etc. In this study, all quantitative T_1 maps were co-registered with post-contrast T_1 -weighted images at 0 weeks. The image registration itself can be confounded by patient reposition and spatial resolution. The patient positioning between two consecutive examinations can have a large effect on the estimated RC values, as the slice positions where the VOIs were drawn might not perfectly match between two studies. One earlier study suggests that position misalignment as small as the slice thickness can cause the same amount of T_1 variation as the repeatability of the whole method (10). Although we were careful to minimize the partial volume effect while drawing the VOIs, it is another inevitable factor causing T_1 variation. Similarly, the transmitted B_1 field inhomogeneity, particularly in the 2FA method, causes deviations in applied flip angles, which in turn can produce T_1 variation. Another major factor affecting the reliability of the estimated RC is the sample size, which will be discussed in the following paragraph. Most interestingly, the VOI size has a limited influence on the RC, suggesting that noise in the image domain is not the dominant factor affecting repeatability of T_1 values measured a few weeks apart.

Another issue that we would like to address is whether the data qualities from the two acquisition methods were comparable. The conventional way of assessing the data quality is to measure the SNR by employing a two-region approach: the ratio of mean signal intensity in the tissue to the SD of noise in the background region (i.e. in air). However, due to the accelerated data acquisition, imaging reconstruction, and regularization, measurement of SNR is very challenging. As the statistical and spatial distributions of noise in parallel imaging do not fulfill the prerequisite for the conventional two-region approach of estimating SNR, this leads to under- or overestimation of SNR (25). We noticed that the “noise level” measured herein in the background region from pSR images increased with TR and signal. This investigation indicates that the “noise” measured in the background is likely due not to the actual noise, but to the artifact and variation arising from parallel imaging and regularization reconstruction. The latter increase with signal intensity. Thus, in order to further examine the data quality between the two methods, we measured the SD of signals from small VOIs (20–30 voxels) drawn in tissue regions of a short TR (100 ms) image, where T_1 contrast is high enough to avoid the tissue heterogeneity, and compared with the mean signal intensity measured at a single central slice image. The mean signal intensities (from three sample studies) produced by the pSR method increased with TR, ranging from 7.01×10^5 to 1.72×10^7 a.u., while for the 2FA method the mean intensities were 7.78×10^7 and 1.47×10^8 a.u. for 15° and 5° flip angles, respectively. The ratio of the mean signal to

the SD of the signal from the small VOI was very similar for the two methods: in the range of 16–36 and 18–39 across the patients for the 2FA and pSR method, respectively, indicating the comparable image qualities produced by the two methods. The spatial variation in signals measured in tissue regions were also affected by artifacts and the variations arising from parallel imaging and regularization, suggesting that the ratio measured herein is not the true SNR. Also, visual inspection did not suggest any severe artifacts in the raw images produced by either method. However, these subtle artifacts affect T_1 quantification and repeatability, which is commonly seen in quantitative images from the state-of-art reconstruction algorithms.

The major limitation of this study is the small number of patients. We included 10 patients who met our criteria: they had a low grade brain tumor or benign tumor, received partial brain RT without chemotherapy, and had no tumor recurrence during 85 week follow-ups. In addition, we used a criterion to only include the VOIs receiving accumulated radiation doses less than 10 Gy at the end of RT (5 Gy at week 3) for test–retest data analysis, which led us to exclude some VOIs from some patients. Finally, one patient had missing T_1 data by the 2FA method, so only the pSR data were used in the analysis. Thus, there is a variation in the sample size for different VOIs with a range of seven to nine samples. Since the RC is largely affected by the random error, which can be reduced by averaging multiple measurements or by increasing the sample size, the RC estimated in such a small sample needs to be interpreted cautiously. Also, the 95% confidence intervals of the estimated RCs show a wide range. Further, we examined the variation in T_1 measurement in normal appearing brain tissues of patients who had low grade brain tumor or benign tumor and received partial brain RT. Although we carefully selected the VOIs far from the tumors and ensured accumulated radiation doses in the regions of less than 5 Gy, the impact of brain pathology and physiological conditions of these patients on the repeatability of T_1 values is not known. It is worth pointing out that it is important to obtain the repeatability data from these patients, for whom the treatment response is usually evaluated 2–3 weeks after starting treatment. RC estimated from the healthy volunteers might be lower, due to their different physiological conditions, compared with those from the patients. Further, the test–retest data used in this study are not acquired in a short time interval, e.g. within 24 h, with the expectation that there are no intrinsic physiological changes in analyzed tissue regions over a period of 3 weeks. However, our data provide a different insight into the repeatability of T_1 measurement and may represent a reality in clinical settings, compared with the data observed in healthy subjects with repeated scans within a short time interval.

In conclusion, future studies assessing therapeutic response, by employing the longitudinal changes in native T_1 , could benefit from this study, as it provides a reference value to make a decision on whether an individual change in T_1 is a true change due to a therapeutic effect. Further, a similar repeatability in T_1 measurement produced by the time efficient 2FA method compared with the time consuming pSR method demonstrates that the optimized multi-flip-angle method is desirable to improve the DCE-MRI brain protocols.

Acknowledgments

Research reported in this publication was supported in part by National Institute of Health (NIH), USA grants U01 CA183848 and R01 NS064973. T.L.C. is also supported in part by NIH grants U01 CA166104 and P01 CA85878.

Abbreviations used

2FA	dual flip angles
pSR	progressive saturation recovery
DCE	dynamic contrast enhanced
IR	inversion recovery
VOI	volume of interest
RT	radiation therapy
LL	Look–Locker
SR	saturation recovery
BMS	between-subject mean of squares
WMS	within-subject means of squares
CoV	coefficient of variation
RC	repeatability coefficient
QIBA	Quantitative Imaging Biomarkers Alliance
bSD	between-subject standard deviation
wSD	within-subject standard deviation
SD	standard deviation
SNR	signal–noise ratio

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Figure 1.

T_1 map produced by 2FA to show the VOIs drawn in white matter, frontal (yellow) and parietal (red), and gray matter, putamen (magenta) and thalamus (blue), regions.

Figure 2.

Plot of the percentage change in individual T_1 measurements in each VOI using the 2FA method. Rows from top to bottom: left and right putamen, thalamus, and frontal and parietal white matter, including the percentage change in individual T_1 from 0 weeks to 6 weeks (diamonds), 11 weeks (rectangles), 33 weeks (triangles), and 85 weeks (circles) studies. Two dotted lines in each plot represent the estimated RC interval ($-RC$, RC).

Figure 3.

Plot of the percentage change in individual T_1 measurements in each VOI using the pSR method. Rows from top to bottom: left and right putamen, thalamus, and frontal and parietal white matter, including the percentage change in individual T_1 from 0 weeks to 6 weeks (diamonds), 11 weeks (rectangles), 33 weeks (triangles), and 85 weeks (circles) studies. Two dotted lines in each plot represent the estimated RC interval (-RC, RC).

Table 1

T_1 measurements in VOIs of normal brain tissues acquired by 2FA and SR methods

Parameters	Putamen		Thalamus		Frontal WM		Parietal WM	
	Left	Right	Left	Right	Left	Right	Left	Right
<i>2FA method</i>	<i>n</i> = 8	<i>n</i> = 7	<i>n</i> = 7	<i>n</i> = 7	<i>n</i> = 7	<i>n</i> = 7	<i>n</i> = 8	<i>n</i> = 8
Mean T_1 ($\pm$ SD) ms at 0 weeks	1391 ($\pm$ 66)	1438 ($\pm$ 72)	1640 ($\pm$ 141)	1585 ($\pm$ 96)	820 ($\pm$ 44)	834 ($\pm$ 52)	875 ($\pm$ 89)	879 ($\pm$ 134)
Mean T_1 ($\pm$ SD) ms at 3 weeks	1389 ($\pm$ 47)	1407 ($\pm$ 70)	1647 ($\pm$ 83)	1615 ($\pm$ 110)	819 ($\pm$ 75)	855 ($\pm$ 91)	907 ($\pm$ 87)	906 ($\pm$ 125)
Mean diff. T_1 ($\pm$ SD) ms	-2 ($\pm$ 73)	-31 ($\pm$ 71)	7 ($\pm$ 93)	30 ($\pm$ 54)	-1 ($\pm$ 57)	21 ($\pm$ 61)	32 ($\pm$ 60)	24 ($\pm$ 54)
<i>p</i> value: paired <i>t</i> test	0.96	0.29	0.86	0.46	0.96	0.40	0.41	0.25
<i>p</i> value: Wilcoxon's sign test	0.94	0.47	0.69	0.58	0.81	0.38	0.37	0.38
BMS ($\times 10^{-3}$)	2.04	3.71	8.33	6.39	8.83	13.31	17.19	34.09
WMS ($\times 10^{-3}$)	1.19	1.37	1.69	1.79	1.94	2.41	2.72	2.06
<i>F</i> -score	1.7	2.7	4.9	3.6	4.6	5.5	6.3	19.4
<i>pSR method</i>	<i>n</i> = 8	<i>n</i> = 7	<i>n</i> = 8	<i>n</i> = 8	<i>n</i> = 7	<i>n</i> = 7	<i>n</i> = 9	<i>n</i> = 9
Mean T_1 ($\pm$ SD) ms at 0 weeks	1283 ($\pm$ 273)	1307 ($\pm$ 293)	1355 ($\pm$ 295)	1321 ($\pm$ 253)	947 ($\pm$ 148)	913 ($\pm$ 117)	980 ($\pm$ 206)	985 ($\pm$ 230)
Mean T_1 ($\pm$ SD) ms at 3 weeks	1266 ($\pm$ 287)	1258 ($\pm$ 298)	1331 ($\pm$ 314)	1387 ($\pm$ 327)	946 ($\pm$ 160)	912 ($\pm$ 132)	992 ($\pm$ 224)	999 ($\pm$ 259)
Mean diff. T_1 ($\pm$ SD) ms	-17 ($\pm$ 66)	-49 ($\pm$ 111)	-24 ($\pm$ 100)	66 ($\pm$ 106)	-1 ($\pm$ 38)	-1 ($\pm$ 51)	12 ($\pm$ 67)	14 ($\pm$ 49)
<i>p</i> value: paired <i>t</i> test	0.48	0.28	0.52	0.12	0.92	0.94	0.58	0.41
<i>p</i> value: Wilcoxon's sign test	0.47	0.30	0.46	0.11	0.99	0.94	0.99	0.73
BMS ($\times 10^{-2}$)	9.55	10.25	10.02	9.01	5.21	3.60	9.34	12.10
WMS ($\times 10^{-3}$)	1.55	4.20	2.64	3.49	0.74	1.33	1.37	0.94
<i>F</i> -score	61.4	24.4	38.0	25.8	70.5	27.1	68.0	129.1

n shows the sample size; BMS and WMS, stand for between- and within-subject means of squares and F-score is the ratio of BMS to WMS.

Table 2

Repeatability coefficients (RC_L , RC_U) of T_1 measurement in normal brain tissues produced by 2FA and pSR methods

VOIs	2FA method			pSR method		
	Large	Small	Ratio*	Large	Small	Ratio*
Left putamen	9.7 (6.5, 18.5)	9.6 (6.5, 18.3)	1.0	10.9 (7.4, 20.9)	11.6 (7.8, 22.2)	1.1
Right putamen	10.2 (6.8, 20.8)	13.9 (9.2, 28.2)	1.4	17.9 (11.9, 36.5)	18.3 (12.1, 37.2)	1.0
Left thalamus	11.4 (7.5, 23.2)	13.6 (9.0, 27.7)	1.2	14.2 (9.6, 27.3)	16.6 (11.2, 31.8)	1.2
Right thalamus	11.7 (7.8, 23.9)	14.7 (9.7, 29.8)	1.3	16.4 (11.1, 31.4)	16.4 (11.0, 31.3)	1.0
Mean RC ($\pm$ SD)	10.8 ($\pm$ 1.0)	12.9 ($\pm$ 2.3)	1.2 ($\pm$ 0.2)	14.9 ($\pm$ 3.0)	15.7 ($\pm$ 2.9)	1.1 ($\pm$ 0.1)
Left frontal WM	12.2 (8.1, 24.8)	13.8 (9.1, 28.1)	1.1	7.5 (5.0, 15.3)	7.1 (4.7, 14.4)	0.9
Right frontal WM	13.6 (9.0, 27.7)	14.3 (9.5, 29.1)	1.1	10.1 (6.7, 20.5)	10.8 (7.2, 22.0)	1.1
Left parietal WM	14.5 (9.8, 27.8)	18.3 (12.4, 35.1)	1.3	10.3 (7.1, 18.7)	9.0 (6.2, 16.4)	0.9
Right parietal WM	12.6 (8.5, 24.1)	12.1 (8.3, 22.0)	1.0	8.5 (5.8, 15.5)	6.6 (4.5, 12.1)	0.8
Mean RC ($\pm$ SD)	13.2 ($\pm$ 1.0)	14.6 ($\pm$ 2.6)	1.1 ($\pm$ 0.1)	9.1 ($\pm$ 1.3)	8.5 ($\pm$ 2.0)	0.9 ($\pm$ 0.1)
Overall mean RC ($\pm$ SD)	12.0 ($\pm$ 1.6)	13.8 ($\pm$ 2.5)	1.2 ($\pm$ 0.1)	12.0 ($\pm$ 3.8)	12.1 ($\pm$ 4.5)	1.0 ($\pm$ 0.1)

* Ratio of RC in small to large VOIs.