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Increasing the speed of relaxometry-based compartmental analysis experiments in STEAM spectroscopy

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Abstract

In this work we present a method for improving the speed of spin–spin relaxation time (T_2) measurements for compartmental analysis in stimulated echo localized magnetic resonance spectroscopy without reducing the sampling density. The technique uses a progressive repetition time (TR) to compensate for echo time (TE) dependent variations in saturation effects that would otherwise modulate the received signal at short TRs. The method was validated in T_2 studies on 10 young healthy subjects in spectroscopic voxels localized along either the right or left Sylvian fissure ($2 \times 2 \times 1.5$ cm^3, 10 ms mixing time (TM), 2048 data points, 819.2 ms acquisition time). The TR was automatically adjusted so that TR–TM–TE/2 was kept constant as the TE was incremented. Compared to long TR T_2 experiments, the progressive TR technique consistently replicated the T_2 relaxation times and reference signals of the tissue water compartment while reducing the data acquisition time by more than 50%. The percent error was on average less than 2% for estimates of T_2 and S_0 for the tissue water, an indication that the progressive TR technique is a useful method for determining the tissue water signal for internal referencing.

Keywords: MRS; Transverse relaxation; T_2; Spin–spin relaxation; Spin–lattice relaxation

1. Introduction

Voxel segmentation is an integral part of the quantitation process of single-voxel in vivo ^{1}H magnetic resonance spectroscopy (^{1}H MRS) [1–3]. In ^{1}H MR brain spectroscopy, internal and external referencing schemes use spin–spin relaxometry to separate the volume contributions of tissue water and cerebral spinal fluid (CSF) in a localized volume-of-interest (VOI) to obtain a referencing signal for the calculation of the metabolite concentrations [1–7]. In internal schemes, the tissue water component serves as a reference, while in external schemes the CSF component serves as a measure of CSF partial volume. In the latter case, the CSF component is referenced to an external standard to calculate the tissue volume within the VOI. The presence of both CSF and tissue water within the VOI require a moderate-to-high sampling density to accurately separate the differential relaxation effects of the water compartments. In addition, the long spin–lattice relaxation time (T_1) of CSF typically requires long repetition times to minimize the effects of magnetization saturation on the spin–spin relaxation time (T_2) measurements. These conditions necessitate sparse sampling of the T_2 curve in clinical examinations to minimize patient scan times. Minimal sampling schemes have poor precision and accuracy [8]. In this work, we present a time efficient relaxation measurement technique that uses a variable repetition time (TR) and the acquisition of multiple relaxation curves to reduce the scan time for a stimulated echo (STEAM) spectroscopic T_2 experiment while preserving a high sampling density.

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2. Materials and methods

2.1. A progressive repetition time

A common method for measuring T_2 in in vivo ^{1}H MRS is the repetitive single-echo technique, where the TR is sufficiently long to allow the longitudinal magnetization to fully recovery between repetitions [9]. We will henceforth refer to this method as the fully relaxed T_2 technique. The technique yields a signal S_{XY} from the transverse magnetization that varies as a function of the echo time (TE) as:

$$S_{XY}(\mathrm{TE}_n) = \sum_{m=1}^{M} S_{0\_m} \exp\left(-\frac{\mathrm{TE}_n}{T_{2\_m}}\right), \tag{1}$$

where the summation allows for M different relaxation compartments with various signal contributions S_{0_m}. In the spectroscopic brain model, M is generally restricted to two, CSF and tissue water [1–7]. If the TR is less than five times the T_1 of CSF, then Eq. (1) must be modified to include T_1 saturation effects. For the STEAM sequence, this inclusion yields the familiar equation (Fig. 1) [10–13]:

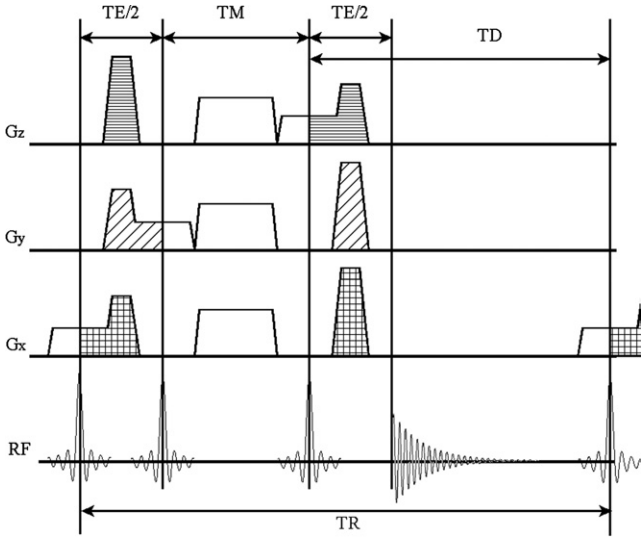

Fig. 1. Schematic of the stimulated echo localization sequence. The mixing time (TM) and delay time (TD) are kept constant throughout each progressive TR experiment. The time interval between the sets of concatenated gradients (positioned before and after the TM period) is kept constant as the TE increases to minimize TM-dependent diffusion-weighting. The concatenation of the refocusing gradient of the first slice-select gradient with the TE spoiler gradient is removed after the dead time during the first TE/2 interval becomes equal to or longer than the length of the RF pulse. This procedure minimizes the diffusion effects from the first slice-select gradient, especially at long echo times, since the rephasing gradient can be applied immediately following slice selection at long echo times.

$$S_{XY}(\mathrm{TE}_n) = \sum_{m=1}^{M} \frac{S_{0\_m}}{2}\left[1 - \exp\left(-\frac{\mathrm{TD}_{n-1}}{T_{1\_m}}\right)\right] \times \exp\left(-\frac{\mathrm{TE}_n}{T_{2\_m}} - \frac{\mathrm{TM}}{T_{1\_m}}\right), \tag{2}$$

where $\mathrm{TD}_n = \mathrm{TR}_n - \mathrm{TM} - \mathrm{TE}_n/2$, and the intervals for TR, TM, and TE/2 are defined in Fig. 1. If Eq. (2) is to be employed for T_2 measurements in a similar fashion as Eq. (1), then the following three conditions must be satisfied: (i) TM must be kept constant, (ii) diffusion-related signal attenuation must also be constant or negligible [14], and (iii) the focus of this work, TD must be kept constant by progressively changing the TR with the TE so that saturation effects are also kept constant. Thus representative T_2 curves of Eqs. (1) and (2) will differ in intensity but not in decay rate.

Compared to the fully relaxed T_2 technique, a relaxometry experiment with a short and progressive TR will yield estimates of the T_2 and T_1-weighted S_{0_m} values. To obtain the true reference S_{0_m} values needed in metabolite concentration calculations, two progressive TR relaxometry experiments with different TD values must be performed so that Eq. (2) can be employed. Although this requires two sets of data, because the minimum TR for a fully relaxed T_2 experiment in the brain is 9 s or greater, T_2 experiments with a progressive TR can be performed considerably faster.

2.2. Relaxometry experiments

To validate the progressive TR technique, spectroscopic relaxometry data were collected from 10 healthy young volunteers using STEAM (4 men/6 women, mean age: 23.5 ± 3.9 years, range: 18–33 years). All experiments were performed on a 1.5 T Magnetom Sonata whole-body MRI system (Siemens Medical Systems, Iselin, NJ) using a standard Siemens circularly polarized proton head coil. Human studies were performed under protocols approved by the institutional review board and with the signed and informed consent of each participant. Each participant underwent a fully relaxed T_2 experiment with TM/TR = 10 ms/11 s, a homospoil saturation recovery (HSR) T_1 experiment [15], two progressive TR T_2 experiments (Table 1), and then a repeat of the fully relaxed T_2 experiment, in that order. The second fully relaxed T_2 data were collected to determine whether a participant had significantly moved during the scan.

The HSR sequence was created by inserting a variable delay time between a three-pulse frequency-selective water suppression preparation sequence and the first slice-selective RF pulse in the STEAM sequence. The progressive TR T_2 sequence was created by inserting variable delay times in the TE/2 periods and at the end of the sequence. The variable delay

Table 1
Echo times, repetition times, and delays time for the STEAM relaxometry studies

TE (ms)	TR (ms)	TD (ms)
Study I		
10.0	1615.0	1600.0
14.0	1617.0	1600.0
20.0	1620.0	1600.0
27.0	1623.5	1600.0
38.0	1629.0	1600.0
53.0	1636.5	1600.0
74.0	1647.0	1600.0
104.0	1662.0	1600.0
145.0	1682.5	1600.0
202.0	1711.0	1600.0
282.0	1751.0	1600.0
394.0	1807.0	1600.0
551.0	1885.5	1600.0
769.0	1994.5	1600.0
1074.0	2147.0	1600.0
1500.0	2360.0	1600.0
Study II		
10.0	3215.0	3200.0
12.0	3216.0	3200.0
17.0	3218.5	3200.0
23.0	3221.5	3200.0
32.0	3226.0	3200.0
45.0	3232.5	3200.0
63.0	3241.5	3200.0
88.0	3254.0	3200.0
122.0	3271.0	3200.0
171.0	3295.5	3200.0
239.0	3329.5	3200.0
334.0	3377.0	3200.0
466.0	3443.0	3200.0
651.0	3535.5	3200.0
909.0	3664.5	3200.0
1500.0	3960.0	3200.0

The TM was fixed at 10 ms for all experiments. The progressive TR experiments were done in two stages: first with the TE and TR values in Study I, and then with the TE and TR values in Study II. The TE values in the fully relaxed experiments were the same as in Study I but with an 11 s TR.

at the end of the sequence was automatically adjusted to keep the TD constant relative to the initial values for TRs of 1615 and 3215 ms, and a 10 ms TE. The weakest four signals in each of the relaxometry experiments were averaged four times to improve the signal-to-noise ratio (SNR) at long echo times in the T_2 experiments and at short recovery periods in the HSR experiments.

Localized voxels were prescribed from three orthogonal sets of multi-slice T_1-weighted gradient-echo images (TE = 4.5 ms, TR: 395–510 ms, 192×256 matrix, 87° flip angle, and 4 mm thick slices). A $2 \times 2 \times 1.5$ cm^3 stimulated echo localized voxel was placed along either the left (7 studies) or right (3 studies) Sylvian fissure. The TM was fixed at 10 ms, while the TR and TE varied as necessitated by the various relaxometry experiments. The TE, TR, and TD values for the T_2 experiments are listed in Table 1. Eight preparatory pulses were applied at the beginning of the progressive TR studies and during the transition between different TD values to ensure steady-state conditions, especially at the margins of the VOI where the flip angles are smaller than 90°. Data sampling consisted of 2K complex data points acquired within an 819.2 ms acquisition window. With an 11 s TR and four prep pulses, each fully relaxed T_2 experiment required 5 min and 40 s. The HSR T_1 experiment required an additional 1 min and 30 s. In comparison, the total time for the progressive TR T_2 experiments was only 2 min and 46 s, representing a 59% reduction in time.

2.3. Data processing and analysis

All HSR T_1 data and fully relaxed T_2 data were processed as previously reported [16]. Each spectrum was phase corrected, zero-filled to 8K, and fit in the time-domain assuming a superposition of multiple water peaks. The fully relaxed T_2 data were fit with a bi-exponential model, the parameters extracted and employed in a constrained bi-exponential T_1 model for fits to the HSR data. The data from the progressive TR T_2 experiments were fit with the six-parameter model of Eq. (2) using a Marquardt–Levenberg nonlinear regression algorithm provided in Sigma Plot (SPSS, Chicago, IL, USA). Using the averaged results of the fully relaxed T_2 calculations as the reference, the T_1 was calculated for the HSR experiment from the constrained T_1 relaxation model. Results from each fit yielded signal estimates for the tissue water (S_{0_tis}) and CSF (S_{0_CSF}) as well as estimates for their respective T_2 and T_1 values: T_{2_tis}, T_{2_CSF}, T_{1_tis}, and T_{1_CSF}. For comparison with the results from the progressive TR T_2 experiment, the results from the two fully relaxed T_2 experiments were averaged to minimize differences from subject self-repositioning. We calculated the relative error, $|x - x_{ref}|/x_{ref}$, for T_1, T_2, and for the CSF and tissue signals from the progressive TR T_2 experiments using the fitted parameters from the fully relaxed T_2 experiments and the HSR T_1 experiment as references, x_{ref}. To assess patient motion, we compared the T_2 and signal estimates for the CSF and tissue water from the two fully relaxed T_2 experiments by examining the relative difference, $|x_1 - x_2|/((x_1 + x_2)/2)$.

3. Results

Fig. 2 shows typical relaxation curves from a fully relaxed (A) and progressive TR ((B) TD = 1.6 s, (C) TD = 3.2 s) T_2 experiments. The SNR is excellent throughout the entire data sets. Compared to the fully

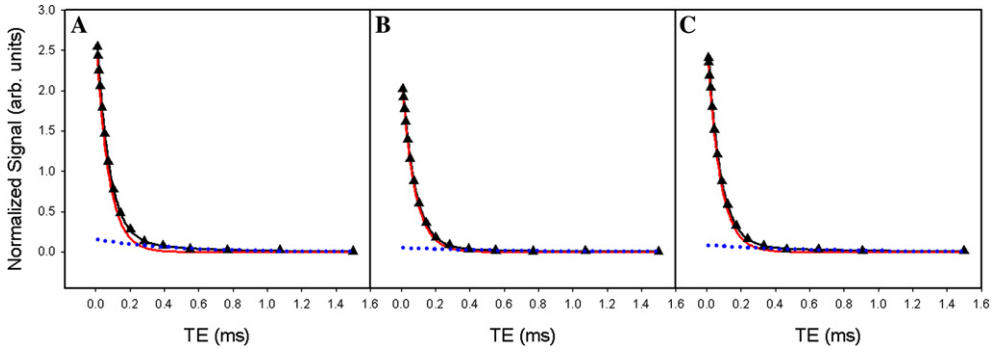

Fig. 2. Representations of T_2 curves from fully relaxed (TR = 11 s (A)) and progressive TR (TD = 1.6 s (B) and TD = 3.2 s (C)) studies show the relative signal intensity differences between the three curves.The (▲) represents the data points, the (——) represents the overall fit from the model, the (— — —) represents the tissue component of the fit, and the (····) the CSF component.

relaxed T_2 study, the maximum signal in the progressive TR T_2 experiment is reduced by approximately 30% when TD = 1.6 s, and only 6% when TD = 3.2 s. Compared to the fully relaxed study, when TD = 1.6 s the tissue signal is reduced by over 18%, but by only 3% when TD = 3.2 s. In comparison, the CSF signal is reduced by nearly 67% when TD = 1.6 s, and 36% when TD = 3.2 s. The CSF signals are strongly saturated even at the longer TD acquisitions. Thus, very long TR values are required in fully relaxed T_2 studies to avoid variable saturation effects of CSF on the overall water signal.

Fig. 3A shows the relative percent difference for S_{0_tis} and T_{2_tis} estimates between the two fully relaxed T_2 experiments. The average difference was only 1.9% for S_{0_tis} and 4.2% for T_{2_tis}. This precision suggests that most subjects moved slightly during the time from the first to the last scan of their relaxometry study and validates averaging the two data sets to create the reference for comparing the progressive TR data.

Figs. 3A–C show the differences between the fully relaxed studies and the progressive TR studies. The progressive TR T_2 experiments consistently replicate the results of the fully relaxed T_2 experiments for the tissue. Individual differences for S_{0_tis} and T_{2_tis} are on average less than 2%. In comparison, the tissue T_1 error is significantly larger with a mean percentage error of almost 10%. The average errors for the CSF parameters are much larger than those of the tissue, ranging from a low of only 8% for the T_{2_CSF} estimate, to nearly 12% for S_{0_csf}, and a high of 54% for T_{1_CSF}. The constrained T_1 technique sometimes yields unrealistically high estimates for T_{1_CSF} with values as high as 9 s long. With none of the T_{1_CSF} values over 5 s long, the progressive saturation technique yields more appropriate values and can thus be regarded as more reliable. Since no HSR T_1 data were acquired in conjunction with the second fully relaxed T_2 experiments, T_1 values were only calculated with the data from the first fully relaxed T_2 experiment in each data set.

4. Discussion

In spectroscopic T_2 segmentation methods, appropriate sampling of the relaxation curve can significantly add to the total experiment time, accounting for as much as 30–50% of the total acquisition time. The progressive TR T_2 technique provides a fast method for measuring T_2. The technique cannot compare in speed to a fast spin–echo sequence (CPMG [9,17]) but is considerably faster than the fully relaxed T_2 measurement technique. The method takes advantage of the intrinsically high SNR of the water peak in single-voxel spectroscopy. With spectroscopic voxels ranging in size from 4 to 8 cm^3, the typical spectroscopy voxel is over a thousand times greater than the typical image voxel. Thus, even at echo times over 1 s, the spectroscopic water signal does not require averaging.

Compared to a fully relaxed T_2 experiment, the progressive TR experiment implemented in this study yields not only estimates of T_2 and S_0, but T_1 as well. Since the progressive TR experiment was employed as a two-point T_1 measurement, the T_1 dependence for each compartment must be modelled by a single exponential. The T_1 sensitivity of the progressive TR technique is limited by the same factors as the standard progressive saturation T_1 technique [18]. The minimum measurable T_1 is approximately one-fourth of the minimum delay time, in this case 1600/4 or 400 ms, which is well below the observed T_1 in brain tissue. The longitudinal magnetization for any T_1 species below this threshold would almost completely recover between excitations (98% M_z) and yield very little T_1 contrast between the two T_2 curves. T_1 values of the tissue water and CSF voxel compartments in the human brain are longer than 400 ms. Over a T_1 range of 400 ms to 2.5 s, the T_1-dependent signal difference between the T_2 acquisitions can vary from a low of only 2% to a high of over 50%, respectively. Compared to inversion recovery and saturation recovery T_1 methods, progressive saturation recovery has a smaller dynamic range that can signifi-

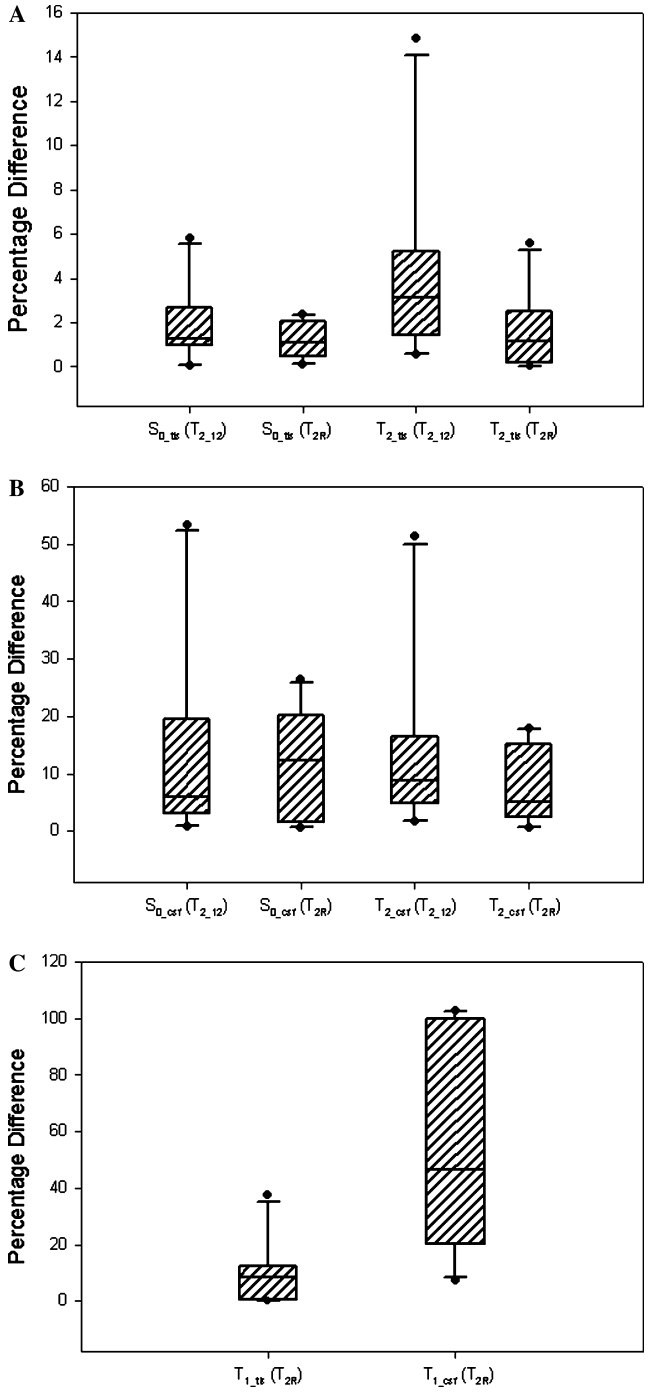

Fig. 3. Box-and-whisker plots show the relative differences between estimates from the two fully relaxed T_2 studies (represented by T_{2_12}) and between the fully relaxed T_2 studies and the progressive TR studies (represented by T_{2R}). The relative differences between the two fully relaxed studies are consistently greater than those between the fully relaxed studies and progressive TR studies; a strong indication that many subjects had moved during the studies. On average the relative differences were smallest for the tissue estimates (A) and largest for the CSF (B). T_1 values for both the fully relaxed and progressive TR experiments differed greatly, especially for T_{1_CSF} with a percent difference greater than 100% (C). Since the HSR experiment was not repeated, no comparisons could be made regarding the effects of patient motion on T_1.

cantly reduce the accuracy and precision of the method [19]. However, contrary to prediction, our progressive TR method shows a better precision than the HSR method. Although additional work is needed to fully understand this phenomenon, we suspect that the improved precision is due to better separation of the CSF and tissue water signal contributions in the bi-exponential model. For a monoexponential model, the greater dynamic range of the HSR technique would likely improve precision, compared to a progressive saturation technique.

Because the progressive TR technique is very precise in reproducing the tissue parameters, this method would be excellent for use in internal water referencing in quantitative brain spectroscopy. This is particularly relevant for receive only coils, where differences in the excitation and reception magnetic fields do not allow a straightforward application of the principle of reciprocity [20]. In this situation, the detected signals must be compared to an external reference signal for absolute quantitation.

5. Conclusions

We have presented a relaxometry technique that uses a progressive TR to reduce the acquisition time of the STEAM T_2 experiment. The method allows a high sampling density to improve separation of the CSF and tissue water compartments that constitute the total water signal in localized spectroscopic voxels in the cerebrum. The progressive TR relaxometry technique might be especially useful for obtaining the T_2 relaxation estimates of the tissue compartment for use in internal water referencing schemes.

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