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## Fast High-Resolution $T_1$ Mapping using Inversion-Recovery Look-Locker Echo-Planar Imaging at Steady State: Optimization for Accuracy and Reliability

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### Abstract

A fast  $T_1$  measurement sequence using inversion recovery Look-Locker echo-planar imaging at steady state (IR LL-EPI SS) is presented. Delay time for a full magnetization recovery is not required in the sequence, saving acquisition time significantly for high-resolution  $T_1$  mapping. Imaging parameters of the IR LL-EPI SS sequence were optimized to minimize the bias from the excitation pulses imperfection and to maximize the accuracy and reliability of  $T_1$  measurements, which are critical for its applications. Compared with the conventional inversion recovery Look-Locker echo-planar imaging (IR LL-EPI) sequence, IR LL-EPI SS method preserves similar accuracy and reliability, while saving 20% in acquisition time. Optimized IR LL-EPI SS provided quantitative  $T_1$  mapping with  $1 \times 1 \times 4$  mm<sup>3</sup> resolution and whole brain coverage (28 slices) in approximately 4 minutes.

### Keywords

Magnetic Resonance Imaging; Fast  $T_1$  measurement; Look-Locker echo planar imaging; steady state; parameter optimization

### Introduction

Fast measurement of spin-lattice relaxation time constant ( $T_1$ ) has been increasingly popular for determining pathology in brain tissues (1–3). Look-Locker echo planar imaging (LL-EPI) sequence has been commonly used for rapid  $T_1$  measurement due to its fast data acquisition (4,5). The coverage of region-of-interest (ROI), spatial resolution, and temporal resolution are important parameters in the design of acquisition paradigms.

A single-shot EPI with a Look-Locker (LL) acquisition can provide a rapid  $T_1$  map within a few seconds (6). Single-shot LL-EPI techniques have limitations when applied to high-resolution (e.g.  $256 \times 256$  in-plane matrix) imaging with multi-slice coverage of the brain. To overcome the loss of temporal sampling points over an inversion recovery (IR) period due to the multi-slice single-shot EPI imaging, an algorithm of reordering the slice acquisitions was proposed (7). However, the spatial resolution was restricted to approximately  $2$  mm<sup>2</sup> ( $128 \times 128$  matrix). Furthermore, these single-shot EPI approaches suffer from geometrical distortions due to magnetic susceptibility differences between tissue and air/bone, and signal loss from a relatively long echo time (TE). Segmented k-space acquisitions have been

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applied to retain the optimal temporal resolution with high spatial resolution (256×256) and/or whole brain coverage (8). However, IR segmented LL-EPI approaches need a delay time between the end of the segmented acquisition at steady state and another inversion pulse for the next segmented acquisition. This delay time for a full recovery of longitudinal magnetization from the steady state is a hindrance for rapid  $T_1$  mapping. To mitigate this problem,  $T_1$  mapping with partial inversion recovery (TAPIR) approach was proposed, which does not require the delay time between segmented acquisitions and the following saturation recovery (SR) pulse (9). However, the additional time between SR and the following IR pulses is still required for high signal-to-noise ratio (SNR). Recent studies proposed that the optimized parameter for the additional time in TAPIR was approximately 2 seconds (10).

We present here a fast  $T_1$  mapping method using a segmented acquisition paradigm of IR LL-EPI, which measures the apparent longitudinal relaxation of magnetization between negative and positive steady states (IR LL-EPI SS). This method does not require the time duration for a full or partial recovery of the magnetization (see Fig. 1), and therefore reduces the total image acquisition time. Potential bias on  $T_1$  measurement due to imperfection of the excitation pulses is investigated, and imaging parameters in the IR LL-EPI SS sequence are optimized with flip angle (FA) of  $16^\circ$ , repetition time (TR) of 400ms, and the time duration in data acquisition per inversion period (TD) of 10s. The accuracy and reliability of  $T_1$  measurements using IR LL-EPI SS are compared with a conventional IR LL-EPI technique using simulation. In the following text, the conventional IR LL-EPI that requires a delay time between successive inversion pulses in the acquisition is referred to IR LL-EPI, and is thus distinguished from IR LL-EPI SS. Phantom studies are performed to validate the  $T_1$  measurement using IR LL-EPI SS and to demonstrate the accuracy and the reliability of the sequence. Finally, high resolution in-vivo  $T_1$  mapping with whole brain coverage (28 slices) is presented with  $1 \times 1 \text{ mm}^2$  in-plane resolution, 4 mm thickness within 4 minutes.

## Methods

### $T_1$ measurement using IR LL-EPI SS

The mathematical model for  $T_1$  measurement using IR LL-EPI sequences has been well investigated in previous studies (5,11). In summary, a longitudinal magnetization as a function of time ( $t$ ) in IR LL-EPI acquisition can be described as

$$M_z(t) \approx M_{SS} - (M_{SS} + M_0)\exp(-t/T_1^*), \quad [1]$$

where  $M_{SS}$  is the longitudinal magnetization in a steady state,  $M_0$  is the equilibrium magnetization, and  $T_1^*$  is the apparent longitudinal magnetization relaxation time constant.

Assuming the transverse magnetization decay following spin-spin relaxation is ignorable ( $T_2 \ll TR$ ),  $1/T_1^*$  can be expressed as

$$1/T_1^* = 1/T_1 - \ln(\cos\theta)/TR, \quad [2]$$

where  $\theta$  is the applied flip angle (FA) and  $TR$  is a time interval between two successive data acquisitions in the same imaging slice.

At steady state,  $M_{SS}$  is expressed as a function of  $M_0$ ,  $TR$ ,  $T_1$  and  $\theta$

$$M_{ss} = \frac{M_0(1 - \exp(-TR/T_1))}{1 - \exp(-TR/T_1)\cos\theta} \quad [3]$$

### The imperfection of the excitation pulses

One of the error sources in the  $T_1$  measurement using IR LL-EPI is the imperfection of the FA of the excitation pulses. The efficiency of the excitation pulses has been investigated and its effects on  $T_1$  measurement has been reported (12,13). When the actual FA is defined as  $\gamma\theta$ , where  $\gamma$  is the efficiency of the excitation pulse, equation [2] can be modified as

$$1/T_{1,m}^* = 1/T_1 - \ln(\cos\gamma\theta)/TR, \quad [4]$$

where  $1/T_{1,m}^*$  is the measured apparent relaxation rate of longitudinal magnetization. However, measured  $T_1$  ( $T_{1,m}$ ) is calculated without considering the efficiency of the excitation pulses,

$$1/T_{1,m} = 1/T_{1,m}^* + \ln(\cos\theta)/TR. \quad [5]$$

Combining equation [4] and equation [5],  $1/T_{1,m}$  can be expressed as

$$1/T_{1,m} = 1/T_1 + \ln(\cos\theta/\cos\gamma\theta)/TR. \quad [6]$$

Therefore, the discrepancy between the measured and true  $T_1$  values due to imperfection of excitation pulses ( $1/T_{1,m} - 1/T_1$ ) can be expressed as a function of  $TR$ ,  $\gamma$ , and  $\theta$ . When an unitless variable,  $\tau_{TR}$  ( $=TR/T_1$ ), is introduced, the accuracy of measured  $R_1$  due to the imperfect excitation ( $A_\gamma$ ) can be expressed as

$$A_\gamma = \frac{1/T_{1,m} - 1/T_1}{1/T_1} = \frac{\ln(\cos\theta/\cos\gamma\theta)}{\tau_{TR}}. \quad [7]$$

A previous study showed that the normalized  $B_1$  histogram over the whole brain has mean efficiency of approximately 90.0% and full width at half maximum of 8.7% (14). Assuming the  $B_1$  histogram follows a normal distribution, the standard deviation (SD) is calculated as 3.69%. Then, 99% of normalized  $B_1$  is expected to have efficiency larger than 81.4%. Using equation [7],  $A_\gamma$  was calculated with two  $\gamma$  values, 0.9 and 0.814, which represent the mean and the lowest 99% of the  $B_1$  efficiency values, respectively, in brain imaging.

**Optimization of accuracy and reliability in the  $T_1$  measurement**—The relaxation of longitudinal magnetization between negative and positive  $M_{SS}$  follows a simple exponential equation over time,  $M_{SS}(1 - 2\exp(-t/T_1^*))$ . When normalized by  $M_{SS}$ , the longitudinal magnetization signal intensity at time  $t$ ,  $S(t)$ , can be expressed simply as  $S(t) = 1 - 2\exp(-t/T_1^*)$ . Using equation [2] and  $\tau_{TR}$ ,  $S(t)$  can be described as

$$S(t) = 1 - 2\exp[-t/T_1 \times (1 - \ln \cos\theta/\tau_{TR})] \quad [8]$$

When the time duration of data acquisition per IR period,  $TD$ , is normalized by  $T_1$ , another unitless variable,  $\tau_{TD} (=TD / T_1)$ , is introduced. Therefore,  $S(TD)$  can be expressed simply as

$$S(TD) = 1 - 2\exp[-\tau_{TD}(1 - \ln(\cos\theta)/\tau_{TR})] \quad [9]$$

Note that equation [9] represents how close the longitudinal magnetization approaches the steady state at time  $TD$ . Figure 2 shows the representative curve of  $S(TD)$  with  $\tau_{TR} = 0.4$ . To allow 99% of the longitudinal magnetization to recover at the end of the IR period,  $\tau_{TD}$  should be larger than 6. Assuming brain  $T_1$  values at 3T are approximately from 1 s (white matter; WM) to 1.5 s (gray matter; GM) (15),  $TD$  values for accurate  $T_1$  measurements in brain tissues should be larger than 9 s. Therefore, the optimal  $TD$  value was chosen as 10 s, and  $\tau_{TD}$  was consequently set to 6.5 in the simulation.

Signal recovery at the acquisition time points was simulated in both IR LL-EPI SS and IR LL-EPI. Monte Carlo simulation (repetition =  $10^4$ ) was performed with various  $\tau_{TR}$  and  $\theta$ . However, the optimal parameters are dependent on SNR in the IR images. The experimental SNR in GM at steady state with a  $90^\circ$  excitation was used as an index, denoted as  $SNR_{SS}(\theta = 90^\circ, GM)$ . Normalized by expected steady-state signal intensity in GM (assuming  $T_1$  value in GM is  $T_{1,GM}$ ), SNR at the steady state with  $90^\circ$  excitation pulses in GM can be written as;

$$nSNR_{SS}(\theta=90^\circ, GM) = SNR_{SS}(\theta=90^\circ, GM) / (1 - \exp(-TR/T_{1,GM})) \quad [10]$$

Experimental noise was added to the simulations as described in (16).

$$\sqrt{(M+n_1/SNR)^2 + (n_2/SNR)^2} \quad [11]$$

Where,

$$M = 1 - (M_i + 1)\exp\{-(n+t_i/TR) \times (\tau_{TR} - \ln(\cos\theta))\} \quad [12]$$

$$SNR = (1 - \exp(-\tau_{TR}))\sin\theta / (1 - \exp(-\tau_{TR})\cos\theta) \times nSNR_{SS}(\theta=90^\circ, GM) \quad [13]$$

In the above equations,  $M_i$  is the initial longitudinal magnetization normalized by the signal intensity at steady state, and was set to 1 for the simulation of IR LL-EPI SS and  $M_0 / M_{SS}$  for IR LL-EPI. Parameters,  $n_1$  and  $n_2$  are randomly chosen numbers from a Gaussian distribution with zero mean and unit variance.  $n$  is an integer ranging from 0 to  $\tau_{TD} (6.5) / \tau_{TR}$ . The time interval between the inversion pulse and the first acquisition pulse ( $t_i$ ) was set to a half of  $TR$  in the simulation.  $SNR_{SS}(\theta = 90^\circ, GM)$  was measured as 28 from a representative GM ROI in the experimental data with whole brain coverage, acquired with a  $256 \times 192$  cm<sup>2</sup> FOV,  $256 \times 192$  in-plane matrix, 4mm thickness,  $TR/TE = 400/6.2$  ms, and  $FA = 90^\circ$ .  $T_{1,GM}$  was set to 1.5 s in the simulations based on previous studies (15).

Using equations [10–13], MR signals at the acquisition time points were simulated with varying  $TR$  and  $FA$ . The simulated signal recovery data were fitted to a three-variable mono-exponential equation, using a Levenberg-Marquardt fitting algorithm (MATLAB 7.5, Mathworks, Inc., Natick, MA). Note that the signals were simulated following Eq.[12], therefore  $\tau_{TR}$  (rather than  $T_1$ ) was obtained from the fitting.

The accuracy of the  $R_1$  measurement using IR LL-EPI SS,  $A_{IRLLEPISS}$ , was defined as  $(1/T_{1,IRLLEPISS} - 1/T_{1,true})/(1/T_{1,true})$ . When TR is multiplied by both nominator and denominator terms,  $A_{IRLLEPISS}$  can be calculated by  $\tau_{TR}$  values:

$$A_{IRLLEPISS} = (\tau_{TR,IRLLEPISS} - \tau_{TR,true}) / \tau_{TR,true} \quad [14]$$

Reliability (or error) of the  $R_1$  measurement using IR LL-EPI SS was evaluated by the SD of the fitted  $\tau_{TR}$  normalized by the simulated  $\tau_{TR}$  value

$$rSD_{IRLLEPISS} = SD_{IRLLEPISS} / \tau_{TR,true} \quad [15]$$

For comparison, accuracy ( $A_{IRLLEPI}$ ) and reliability ( $rSD_{IRLLEPI}$ ) of an IR LL-EPI approach, defined similarly as those of IR LL-EPI SS, were also calculated.

### Phantom and in vivo experiments

The accuracy and the reliability of both IR LL-EPI SS and IR LL-EPI approaches were demonstrated in phantom studies. Six phantoms containing different concentrations of Gadolinium solution based on distilled water (0.05, 0.075, 0.1, 0.2, 0.3, and 0.4 m Mol/L) were prepared. MRI scans were performed on a Siemens 3T Allegra scanner (Siemens Medical Solutions, Erlangen, Germany). For measurement of the intrinsic  $T_1$  of the phantoms, data were collected using a single-slice, non-selective IR EPI sequence with 10 different inversion times (TIs) ranging from 34 ms to 15000 ms. TR was set to 30 s, sufficient for the full recovery of the longitudinal magnetization, and TE was set to 11 ms. The other imaging parameters were: FA=16°, FOV=256×192 mm<sup>2</sup>, matrix=64×48, 4mm thickness (voxel size=4×4×4mm<sup>3</sup>). To minimize potential instrumental instability and the effects of temperature fluctuation due to repeated RF pulses, the intrinsic  $T_1$  values of the phantoms were measured twice before and after IR LL-EPI SS and IR LL-EPI scans, and the two measurements were averaged.

The phantoms scans were repeated 10 times with non-selective IR LL-EPI SS and IR LL-EPI sequences in an interleaved order. The center slice of the multi-slice IR LL-EPI SS or IR LL-EPI was aligned to the single slice of the IR EPI imaging acquired for the intrinsic or baseline measurement as described above. Optimal imaging parameters for the LL sequences were determined from the simulations: FA=16°, FOV=256×192 mm<sup>2</sup>, matrix=256×192, 4mm thickness (voxel size=1×1×4mm<sup>3</sup>), 28 slices, bandwidth = 1628 Hz/voxel, TR/TE = 400/6.2 ms, number of lines in k-space per data acquisition = 9, TD= 10 s. An additional delay time of 3 s was inserted for the IR LL-EPI scan before the repeated inversion pulses. Total acquisition time of IR LL-EPI SS and IR LL-EPI were 4 minutes and 5 minutes, respectively.  $T_1$  values of the phantoms in the center slice of LL approaches were measured and compared with  $T_1$  values measured with IR EPI in six selected ROIs, each encompassing a different tube (note that the center slice of LL approaches is positioned same as the single slice of IR EPI). The accuracy of both LL methods was calculated assuming  $T_1$  values measured with IR EPI as baseline. The reliability of both LL methods was assessed by calculating the average SD values in the six ROIs across the 10 LL measurements.

Three healthy subjects were scanned using the non-selective IR LL-EPI SS sequence with the same imaging parameters as in the phantoms. For the validation of  $T_1$ , the same IR EPI scan was performed as that in the phantom experiment above. Written informed consent was obtained from the participants prior to the experiments in accordance with the protocol approved by the Institutional Review Board of the National Institute on Drug Abuse.

## Results

Figure 3 shows the accuracy of  $R_1$  measurement of IR LL-EPI SS with excitation efficiencies of 0.9 and 0.814, respectively. When  $\tau_{TR}$  is larger than 0.25, the error is within 5% for  $\gamma=0.9$  and  $FA \leq 20^\circ$ , and for  $\gamma=0.814$  and  $FA \leq 16^\circ$ . The bias from the excitation pulse imperfection increases when larger FA and shorter  $\tau_{TR}$  (or TR) are applied.

From the result of Monte-Carlo simulation, the accuracies of  $R_1$  measurements, averaged across different  $\tau_{TR}$  values using IR LL-EPI SS and IR LL-EPI are listed in Table 1. It is shown that the accuracies of the two methods ( $A_{IRLLEPISS}$  and  $A_{IRLLEPI}$ ) are similar, both below 1 % error when FA ranges from  $8^\circ$  to  $32^\circ$ . Figure 4 depicts the reliability of  $R_1$  measurements for both LL methods. When  $\tau_{TR} > 0.2$ , the reliability plots of the two methods are very similar, showing a trend of improved reliability at larger FAs. However, the reliability of IR LL-EPI SS at lower  $\tau_{TR}$  ( $\tau_{TR} < 0.2$ ) is worse than that of IR LL-EPI, especially for larger FAs.

To maximize the accuracy and reliability and to minimize the bias from the excitation imperfection, the optimal FA was determined by analyzing Fig.3 and Fig.4. FA of  $16^\circ$  was chosen by minimizing  $|A_\gamma| + 2.33 \cdot |rSD|$  in the range of  $0.25 \leq \tau_{TR} \leq 0.4$ . Figure 5 shows the accuracy and reliability of both IR LL-EPI SS and IR LL-EPI as a function of  $\tau_{TR}$  at a FA of  $16^\circ$ . When  $\tau_{TR}$  ranges from 0.25 to 0.4, both IR LL-EPI SS and IR LL-EPI approaches produce high accuracy ( $\sim 0.2\%$  of error) and good reliability ( $4.1 \pm 0.3\%$  and  $3.9 \pm 0.4\%$ , respectively). Assuming typical  $T_1$  for brain tissues ranges from 1 to 1.5 s at 3T, the optimal TR can be determined to be between 300 ms and 400 ms. Because longer TRs can provide shorter scan time for fixed brain coverage, and are less sensitive to bias from the excitation pulse imperfection (see Table 3), TR of 400 ms and FA of  $16^\circ$  were used as the optimal parameters in the following phantom and *in vivo* experiments.

Using the optimized parameters, the accuracy and the reliability of both IR LL-EPI SS and IR LL-EPI approaches were measured in phantoms, and the results are shown in Tab. 2. Assuming  $T_1$  values measured by IR EPI as a baseline, the accuracy of the high-resolution  $T_1$  measurement in both LL methods was within 1.2%, and the reliability of the  $T_1$  measurement was 5.2% for IR LL-EPI SS and 5.0% for IR LL-EPI, across the phantoms with a  $T_1$  range of 688–1970 ms.

A representative high-resolution *in vivo*  $T_1$  mapping using IR LL-EPI SS with a FA of  $16^\circ$  and a TR of 400 ms is shown in Fig. 6. The total acquisition time covering 28 slices was 4 minutes, or about 8.6 s per slice. Fig. 7 shows a comparison between  $T_1$  maps using IR EPI ( $64 \times 48$  matrix) and IR LL-EPI SS ( $256 \times 192$  matrix). Three ROIs were drawn manually in representative regions of WM, GM and CSF. The  $T_1$  values were  $943 \pm 57$ ,  $1460 \pm 33$ , and  $4391 \pm 545$  ms in WM, GM, and CSF, respectively, as measured by IR EPI.  $T_1$  values measured by IR LL-EPI SS were  $964 \pm 116$ ,  $1465 \pm 148$ , and  $4522 \pm 417$  ms in WM, GM, and CSF, respectively. The two methods showed consistent results, which are also in good agreement with the literature (15,17).

## Discussion

The basic approach to calculate  $T_1$  from a train of LL-EPI acquisitions after an inversion or saturation pulse is to fit the data to an exponential equation, such as  $A - B \times \exp(-t/T_1^*)$ . Two distinct methods have been proposed measuring  $T_1$  using IR LL-EPI. The first method is to calculate  $T_1$  from the measured signal regrowth rate  $1/T_1^*$  with FA and TR as input variables (see Eq. [2]) (5,13). The other method uses the measured  $T_1^*$  and the ratio of  $M_0$  to  $M_{SS}$  ( $T_1 = T_1^* \times M_0/M_{SS}$ ) (18). For convenience, the former method which is dependent on

applied flip angle is referred to as the FA dependent method, and the latter as the FA independent method.

Error sources have been investigated for accurate measurement of  $T_1$ . The efficiency (or imperfection) of the inversion pulse has been reported to be an important error source in  $T_1$  measurement. Kingsley et al. demonstrated an imperfect inversion efficiency of 0.85–0.94 in the human brain even with non-selective adiabatic inversion pulses (19). Note that the inversion efficiency invokes directly a proportional bias on  $T_1$  measurement in the FA independent method. To correct for the imperfection of inversion pulses, additional scanning is required. Zaitsev et al. proposed a method to map the inversion efficiency for the  $T_1$  correction by comparing TAPIR sequences with and without a  $180^\circ$ – $180^\circ$  module after a  $90^\circ$  excitation pulse and preparation time (10). It was shown that inversion efficiency was 0.76 to 0.98 in the human brain, and a maximum  $T_1$  error of 24% was observed in the cingulate region when the efficiency was not corrected (10). Imperfection of non-selective adiabatic inversion pulses in the brain is believed to be mainly due to  $B_1$  inhomogeneity and the relatively short  $T_2$  of brain tissue components (19). Therefore, an additional scan is needed for the correction as proposed (10), which makes running time twice as long. In this study, we used FA dependent method for  $T_1$  calculation, which avoided error from  $M_0$  measurement due to inversion efficiency.

The excitation pulse efficiency has also been reported to be an important error source for  $T_1$  measurement when FA was used as an input variable to measure  $T_1$ . Samson et al. showed an overall  $B_1$  efficiency of approximately 0.9 in the human brain (14). Yarnkh demonstrated  $B_1$  variations of 0.88 to 1.04 relative to the nominal  $B_1$  (20). The discrepancy between the actual and the specified FAs is mainly due to  $B_1$  inhomogeneity and slice-profile imperfection. Mapping  $B_1$  inhomogeneity has been used to correct for the bias in  $T_1$  measurement. One of the methods for  $B_1$  mapping is to measure the actual FA using a dual FA sequence (21). Based on measured FA imaging,  $T_1$  correction is feasible (13,22). However, additional scanning is needed for these methods. In the present study, to achieve shorter acquisition time, we used an approach to minimize the bias in  $T_1$  measurement by optimizing imaging parameters, rather than measuring FA maps. Alternatively, IR LL-EPI SS with dual or varying FA could be used to correct for the error in  $T_1$  due to an imperfect FA, although the total scanning time would be increased.

The imaging parameter optimization in LL approaches for fast T1 mapping has been investigated in previous studies (11,23). Crawley and Henkelman derived a relative figure of merit,  $\Gamma = DR / (b \sqrt{T_{seq}})$ , where  $DR$  is the dynamic range,  $b$  is a constant, and  $T_{seq}$  is the duration of the sequence (11). Note that  $DR$  is  $2 \times M_{SS}$  for IR LL-EPI SS, and  $(M_0 + M_{SS})$  for IR LL-EPI. When  $T_{seq}$  is set to 10 s for IR LL-EPI SS, and 13 s for IR LL-EPI, the relative merit of IR LL-EPI SS is improved by approximately 8% compared to IR LL-EPI with  $0.2 < \tau_{TR} < 0.4$ . Kay and Henkelman proposed an optimal FA of  $20^\circ$ , which agrees with our findings (see Fig3-A and Fig.4-B) (23). However, a smaller FA can minimize the bias from the excitation pulses imperfection, which gets severe with low  $\tau_{TR}$  or large T1. In this study, a FA of  $16^\circ$  was chosen as the optimal value. For the simulation results showed that with FA= $16^\circ$ , the accuracy of IR LL-EPI SS and IR LL-EPI are about 0.2% in with  $0.2 < \tau_{TR} < 0.4$ . The reliability of IR LL-EPI is slightly higher than that of IR LL-EPI SS (3.9% vs 4.1%). The phantom experiments showed the similar results. In the phantoms with a  $T_1$  of 650 to 1900 ms, both LL methods possessed similar accuracy (average error  $\sim 1.2\%$ ). IR LL-EPI showed slightly better reliability than IR LL-EPI SS (5.0% vs 5.2%). The slight loss of reliability ( $\sim 5\%$ ) using IR LL-EPI SS can be explained by the discrepancy of  $DR$  between IR LL-EPI SS and IR LL-EPI. The equation derived by Crawley and Henkelman showed that the reliability is proportional to  $DR$  (11). When FA of  $16^\circ$  is applied, the ratio of  $DR$  in IR LL-EPI SS to in IR LL-EPI is 94.8% for  $0.2_1 \tau_{TR} < 0.4$ . However, IR LL-EPI SS reduces

the total acquisition time (4 minutes) by approximately 20% as compared with the IR LL-EPI (5 minutes), when a fixed TD of 10 s is used in both methods and an additional delay time of 3 s is added for a full magnetization recovery in IR LL-EPI.

In this study, the optimal imaging parameters for IR LL-EPI SS were chosen as  $FA=16^\circ$  and  $TR=400$  ms based on the simulations considering the lowest 99% of FA efficiency ( $=0.814$ ) experimental SNR ( $=28$ ) values. However, FA efficiency may dependent on various parameters, such as magnetic field strength, geometry and anatomy of the object, coil type, and characters of the excitation pulse. Therefore, optimization should be performed either on a wider range of RF efficiency or based on specific experiments. For example,  $T_1$  mapping using IR LL-EPI SS with a  $64\times 64$  or  $128\times 128$  matrix size might allow for smaller FA and longer TR values, due to higher SNR, as optimal parameters than high-resolution  $T_1$  mapping ( $256\times 256$ ). Furthermore, optimization is dependent on the considerations of specific studies. In particular, optimal TR is important for fast high-resolution  $T_1$  mapping, because it affects the total acquisition time. When the brain coverage or the number of imaging slices is fixed, a longer TR value allows a larger number of k-space lines readout per acquisition, which leads to less segmentation to fill the k-space, and therefore reduces the total running time. Tab. 3 shows three sets of imaging parameters and the corresponding accuracy and reliability in the range of WM and GM for 28 slices of IR LL-EPI SS scanning, with TR of 300, 400 and 500 ms. These parameters provide similar accuracy across a range of  $\tau_{TR}$  corresponding to  $T_1$  values of WM and GM. Relative to the results at  $TR=400$ ms, 300 ms TR gives a 9% improvement in reliability, and 500 ms TR losses 10% of reliability. However, the total running time increases by 66% with 300 ms TR, and decreases by 21% with a 500ms TR, compared to 400 ms TR. Fig. 8 compares a representative slice of  $T_1$  map from a subject when different TR values were applied. The enlarged  $T_1$  maps in the bottom row show that the  $T_1$  maps look slightly grainier when TR values are increased. However, the loss of reliability in the  $T_1$  map is not dramatic among 300, 400 and 500 ms, which is in agreement with the simulation results in Tab. 3. While a TR of 400 ms is considered optimal in this study, the optimization of TR values might depend on the priority of specific experiments, in which total running time and reliability are considered.

In summary, fast high-resolution  $T_1$  mapping can be achieved by the IR LL-EPI SS method, which does not require an additional time delay between inversion pulses and therefore shortens the total acquisition time. Imaging parameters of the IR LL-EPI SS sequence were optimized to minimize the bias from the imperfection of excitation pulses and to maximize the accuracy and reliability of  $T_1$  measurement. Compared with IR LL-EPI, the IR LL-EPI SS method preserves similar accuracy and reliability, while saving 20% in acquisition time. The proposed fast  $T_1$  mapping technique was demonstrated on in vivo human brains, and provided an imaging time of 8.6 s per slice.

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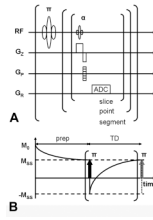
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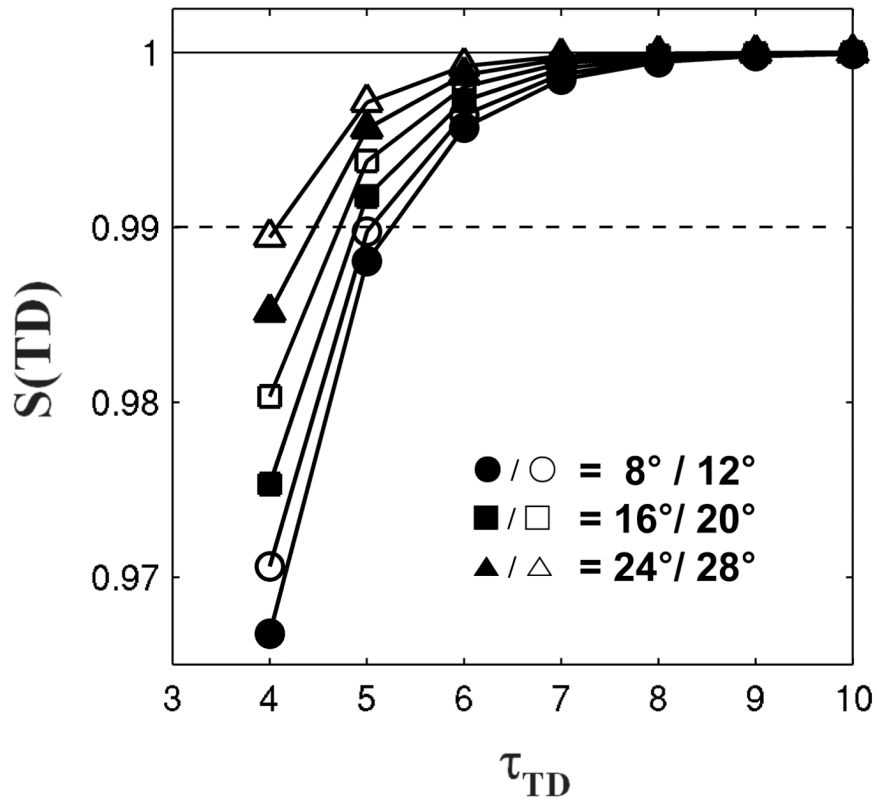


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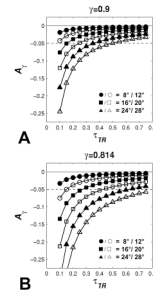
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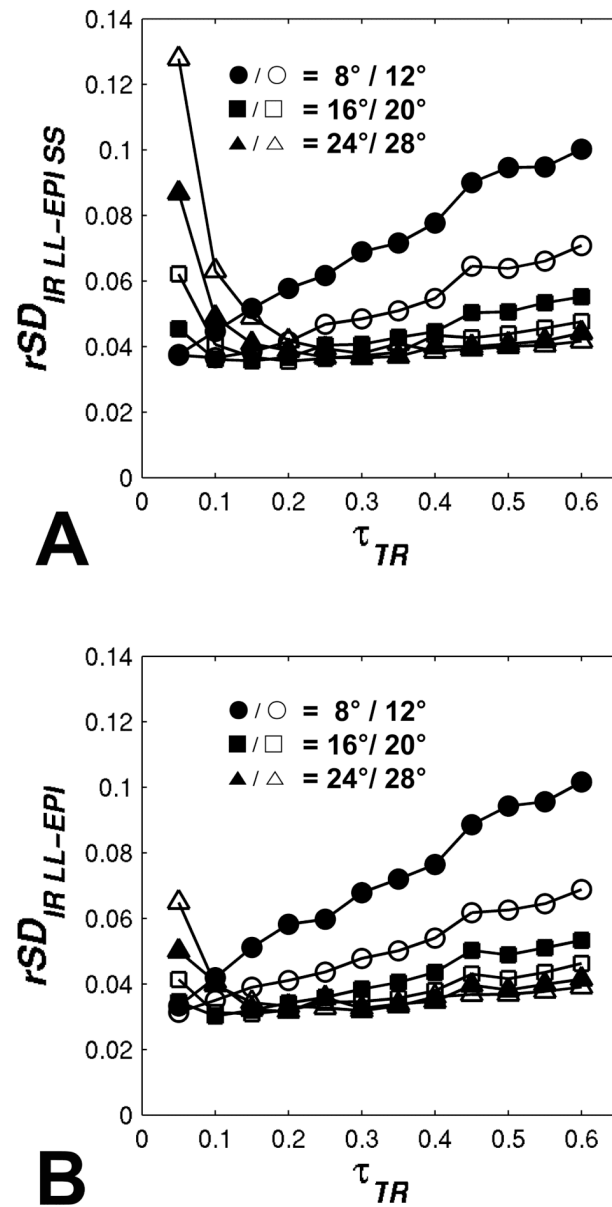
**FIG 1.** IR LL-EPI SS sequence diagram (A) and acquisition paradigm (B). After a non-selective inversion pulse, a series of  $\alpha^\circ$  excitation RF pulses are applied to acquire partial k-space data (ADC) following the LL acquisition algorithm. Before the first inversion pulse and data acquisition, a series of  $\alpha^\circ$  preparation pulses (prep) are applied for TD to make the longitudinal magnetization in each imaging plane approach a steady state.



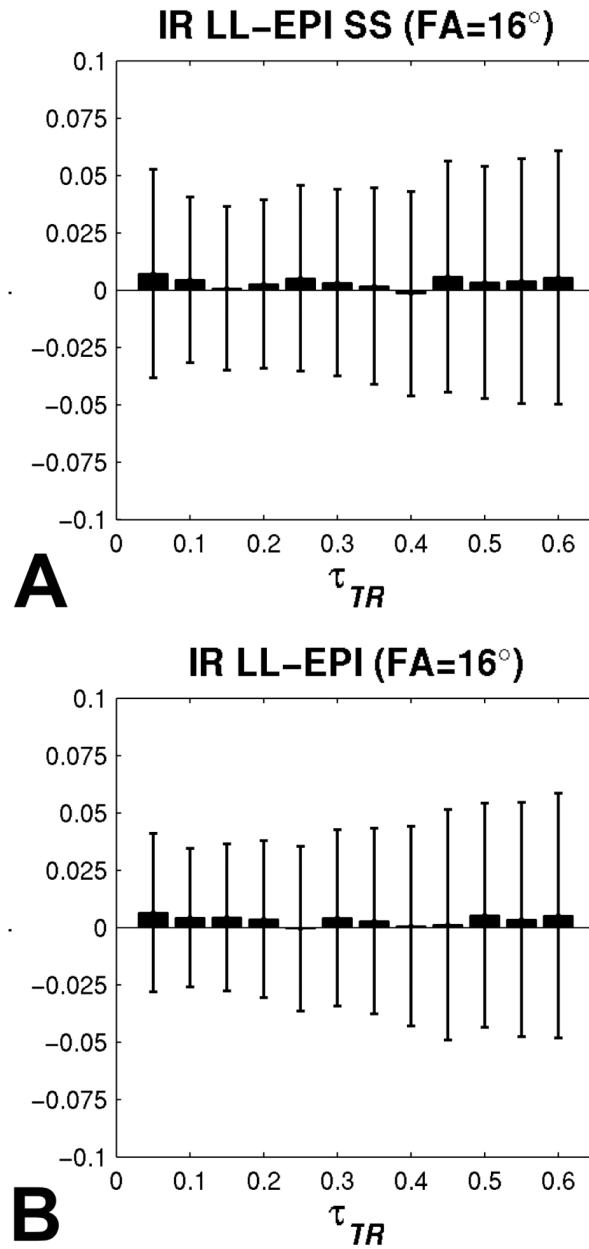
**FIG 2.** Recovery of longitudinal magnetization in an LL sequence as a function of  $\tau_{TD}$ . The relaxation curves show that 99% of the steady-state longitudinal magnetization recovers at the end of the IR period when TD is 6 times longer than expected  $T_1$  values for various FAs. The solid line and dashed line represent 100% and 99% of the steady-state signal respectively.



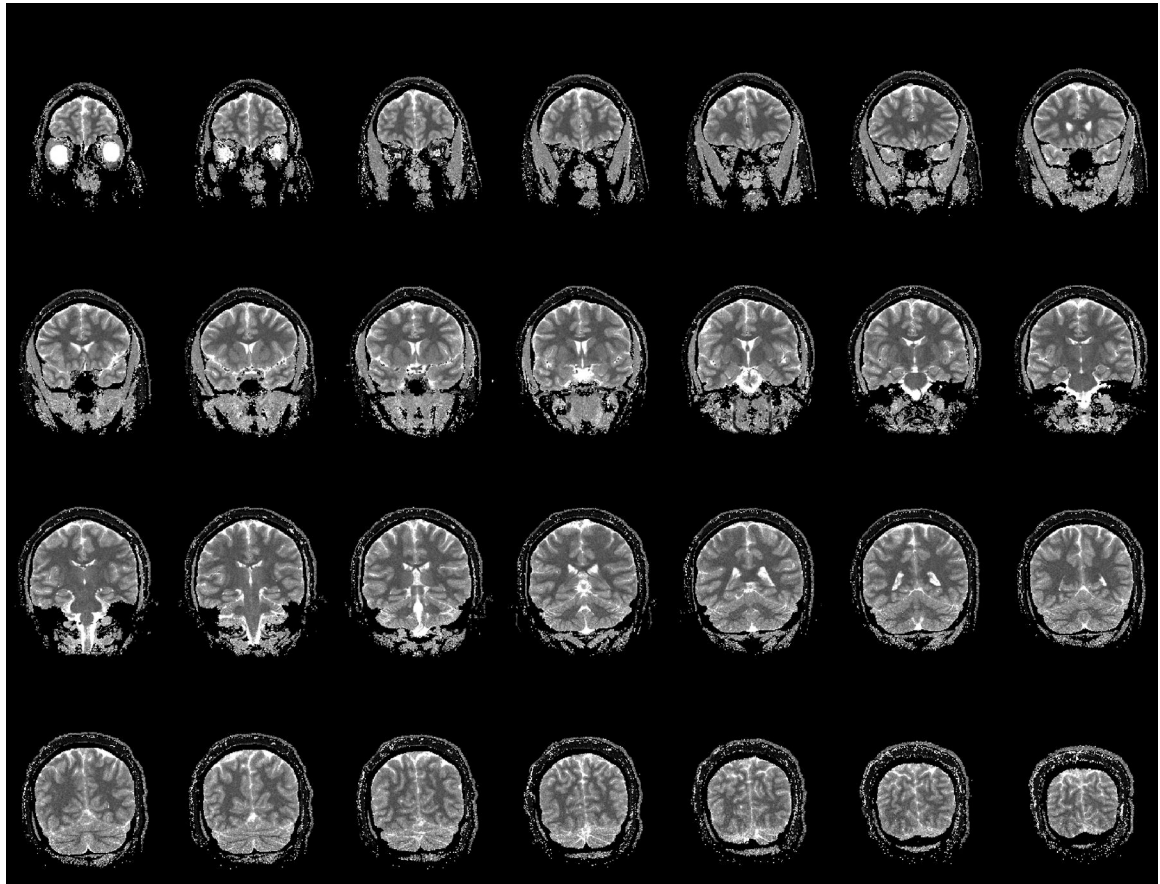
**FIG 3.** The effects of the imperfect efficiency of the excitation pulse on  $T_1$  measurement. Two efficiency values (A: $\gamma=0.9$ , and B: $\gamma=0.814$ ) are simulated. Accuracy as a function of  $\tau_{TR}$  is demonstrated with different FAs, shown as. Dashed lines represent  $\pm 5\%$  of error.



**FIG 4.** Monte Carlo simulation results of the  $R_1$  measurement reliability using (A) IR LL-EPI SS and (B) IR LL-EPI. Different FAs are simulated over varying  $\tau_{TR}$  values.

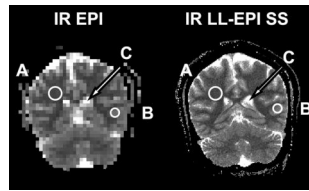


**FIG 5.** The accuracy and reliability of IR LL-EPI SS (A) and IR LL-EPI (B) are compared as a function of  $\tau_{TR}$  when a FA of  $16^\circ$  is applied. Wide solid bars and error bars represent the accuracy and the reliability, respectively, over different  $\tau_{TR}$  values.

**FIG 6.**

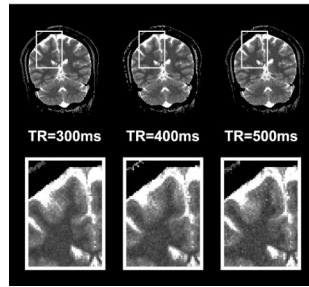
A representative  $T_1$  maps using IR LL-EPI SS. The maps are scaled from 0 (black) to 3500ms (white). 28 slices of high-resolution  $T_1$  mapping ( $1 \times 1 \times 4 \text{ mm}^3$ ) are obtained in 4 minutes with  $\text{FA}=16^\circ$  and  $\text{TR}=400\text{ms}$ .





**FIG 7.**

A comparison of  $T_1$  measurements using IR EPI and IR LL-EPI SS. Representative WM (A), GM (B), and CSF (C) ROIs are drawn as shown in the figure.  $T_1$  values are measured as  $943 \pm 57$ ,  $1460 \pm 33$ , and  $4391 \pm 545$  ms using IR EPI and  $964 \pm 116$ ,  $1465 \pm 148$ , and  $4522 \pm 417$  ms using IR LL-EPI SS in WM, GM, and CSF, respectively.



**FIG 8.**

Representative  $T_1$  maps acquired with TR =300, 400, or 500 ms. The total acquisition time for whole brain  $T_1$  mapping (28 slices) with these parameters is 6min 40s, 4min, or 3min 10s.

**Table 1**

The accuracy of  $R_1$  measurements averaged over different  $\tau_{TR}$  values ( $0.05 < \tau_{TR} < 0.60$ ) using the IR LL-EPI SS ( $A_{IRLLEPISS}$ ) and IR LL-EPI ( $A_{IRLLEPI}$ ).

Accuracy (%)	Flip angle						
	8°	12°	16°	20°	24°	28°	32°
$A_{IRLLEPISS}$	1.0 ± 0.5	0.5 ± 0.3	0.4 ± 0.2	0.4 ± 0.4	0.3 ± 0.3	0.4 ± 0.6	0.5 ± 0.1
$A_{IRLLEPI}$	0.9 ± 0.5	0.5 ± 0.3	0.4 ± 0.2	0.2 ± 0.2	0.2 ± 0.2	0.2 ± 0.3	0.1 ± 0.2

**Table 2**

Accuracy and reliability of IR LL-EPI SS and IR LL-EPI in phantom studies

$T_1$ (ms)	Accuracy (%)			Reliability (%)		
	IR LL-EPI SS	IR LL-EPI	IR LL-EPI SS	IR LL-EPI SS	IR LL-EPI	IR LL-EPI
Tube 1	1.5	0.5	5.7	5.7	5.5	5.5
Tube 2	0.8	0.2	5.2	5.2	5.3	5.3
Tube 3	-1.5	-1.7	5.2	5.2	5.0	5.0
Tube 4	-1.0	-1.3	4.8	4.8	4.7	4.7
Tube 5	-1.2	-1.4	5.3	5.3	4.8	4.8
Tube 6	-3.2	-3.3	5.0	5.0	4.7	4.7

**Table 3**

Accuracy and reliability of IR LL-EPI SS with different TRs.

TR (ms)	lines of readout per acquisition	Total Time (min)	Imaging time per slice (s)	Accuracy (%)	Reliability (%)
300	5	6:40	14.3	0.4±0.1	4.0±0.2
400	9	4:00	8.6	0.2±0.3	4.2±0.2
500	11	3:10	6.8	0.3±0.3	4.6±0.5