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Simultaneous measurement of total water content and myelin water fraction in brain at 3 T using a T_2 relaxation based method

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ABSTRACT

Purpose: This work demonstrates the *in vivo* application of a T_2 relaxation based total water content (TWC) measurement technique at 3 T in healthy human brain, and evaluates accuracy using simulations that model brain tissue. The benefit of using T_2 relaxation is that it provides simultaneous measurements of myelin water fraction, which correlates to myelin content.
Methods: T_2 relaxation data was collected from 10 healthy human subjects with a gradient and spin echo (GRASE) sequence, along with inversion recovery for T_1 mapping. Voxel-wise T_2 distributions were calculated by fitting the T_2 relaxation data with a non-negative least squares algorithm incorporating B_1^+ inhomogeneity corrections. TWC was the sum of the signals in the T_2 distribution, corrected for T_1 relaxation and receiver coil inhomogeneity, relative to either an external water standard or cerebrospinal fluid (CSF). Simulations were performed to determine theoretical errors in TWC.
Results: TWC values measured in healthy human brain relative to both external and CSF standards agreed with literature values. Simulations demonstrated that TWC could be measured to within 3–4% accuracy.
Conclusion: In vivo TWC measurement using T_2 relaxation at 3 T works well and provides a valuable tool for studying neurological diseases with both myelin and water changes.

1. Introduction

Total water content (TWC) mapping is useful to assess changes in water such as edema and inflammation which can occur in many neurological disorders, including stroke, brain tumors, head trauma, multiple sclerosis and hepatic encephalopathy [1–8]. Changes in TWC can also impact the accuracy and interpretation of other MRI measures. Myelin water imaging based on multi-component T_2 relaxation is valuable for investigating neurological diseases such as multiple sclerosis (MS), schizophrenia, phenylketonuria and Alzheimer's disease [9–11,6,12–16]. The myelin water fraction (MWF), defined as the ratio of the myelin water signal (15 ms < T_2 < 40 ms) to the total water signal [17], correlates strongly with histological staining for myelin [9,18–20]. However, it is also affected by changes in the TWC, which can occur with edema or inflammation [21]. In order to isolate changes in MWF due to myelin alone, it is therefore also necessary to measure TWC; simultaneous measurement of these two quantities could provide valuable insight into pathology. Furthermore, multi-component T_2 relaxation enables estimation of CSF content, which is particularly useful for metabolite concentration estimation in MRS.

Several successful MR TWC mapping methods have been developed in the past, the majority at 1.5 T or lower fields [22–26]. As we move to higher magnetic field for improved signal to noise ratio (SNR), increased RF field inhomogeneities make it difficult to achieve accurate signal detection both inside and outside of the brain, and necessitate corrections for both transmit (B_1^+) and receive (B_1^-) inhomogeneity in order to accurately map TWC. A few relatively accurate methods for measuring TWC have been developed at 3 T [27–33]; however, they do not offer the additional myelin water information. Another method for simultaneous TWC and MWF measurement based on T_2^* relaxation was published previously, but the use of T_2^* relaxation meant that myelin water content measurements could be impacted by B_0 inhomogeneity, and large statistical errors in estimated myelin water contents resulted from the low SNR and sparse sampling of the T_2^* decay curve [34,35].

Here we present a method for simultaneous measurement of TWC and MWF at 3 T using T_2 relaxation, which is based on a previous 1.5 T method [24], but features a number of improvements. For one, a faster combined gradient and spin echo (GRASE) sequence was used

Abbreviations: CSF, Cerebrospinal fluid; EPG, Extended phase graph; GRASE, Gradient and spin echo; IE, Intra- and extracellular; MWF, Myelin water fraction; NNLS, Non-negative least squares; RF, Radiofrequency; SD, Standard deviation; SNR, Signal to noise ratio; TWC, Total water content.

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to achieve full cerebrum coverage in 15 min [36], and additional corrections for B_1 inhomogeneity were employed. This technique has previously been validated in phantoms and simulations and has been shown to measure TWC to within 3% accuracy [37], and a similar method using a multi- spin echo T_2 relaxation sequence was used to assess changes in brain water with hydration [38]. In this work, we present *in vivo* results using the faster GRASE sequence in healthy human brain, demonstrate reproducibility in one subject, and compare the use of two water standards for absolute water quantification — a flexible water container placed outside the head, and CSF in the ventricles.

2. Material and methods

2.1. MRI experiment

All experiments were performed on a Philips Achieva 3.0 T MR scanner with an 8 channel phased-array head coil for reception and the internal quadrature bird-cage body coil for transmission. The MRI protocol consisted of a 32 echo 3D GRASE sequence [36] for T_2 measurement (TE_1 and echo spacing = 10 ms, TR = 1 s, 20 5 mm thick slices reconstructed to 40 2.5 mm slices, slice oversampling factor = 1.3, EPI factor 3, axial orientation, SENSE = 2; right/left FOV was adjusted for each subject, so acquired matrix varied from 232 × 226 to 232 × 240, reconstructed matrix = 240 × 240, in-plane voxel size ~1 × 1 mm, receiver bandwidth = 151 Hz, acquisition time = 15-16 min). An inversion recovery (IR) prepared MPRAGE was collected to measure T_1 (5 TIs (150-3500 ms), TR/TE = 6.5/3.2 ms, TFE = 120, shot interval = 5 s, FA = 10°, 13 slices at 5 mm thickness, 256 × 256 matrix, in-plane voxel size approximately 0.9 × 0.9 mm, axial orientation, acquisition time = 6 min) [39]. The body coil sensitivity map acquired for SENSE (a spoiled gradient echo (SPGR) scan with FA = 1°, TR/TE = 4.0/0.8 ms, 100 slices 3 mm thick, matrix = 96 × 75, 5x7mm voxel size, coronal orientation, acquisition time = 44 s) was used to generate a B_1^- map.

2.2. Subject information

10 healthy volunteers (5 male, age 19–66 years) were scanned with a flexible water container (Outbound 2L Bladder Water System, Infinity Sports, Vancouver, BC) placed behind the head as an external water standard. One subject was scanned again 1.5 months later in order to test reproducibility. This study was approved by our institution's Clinical Ethics Review Board and all subjects provided signed, informed consent before participating.

2.3. Post processing and analysis

IR and B_1^- data were registered to the GRASE using FSL's FLIRT tool (default cost function, (between-modality correlation ratio, "corratio"), and 6 degrees of freedom) [40]. FSL's FAST tool was used to create white matter (WM) and grey matter (GM) masks from the TI = 150 ms (WM) and TI = 1500 ms (GM) images [40]. Five GM (thalamus, head of the caudate nucleus, cortical grey, cingulate gyrus, putamen) and five WM (genu of the corpus callosum, major forceps, minor forceps, posterior internal capsules, splenium of the corpus callosum) regions of interest (ROIs) were manually outlined bilaterally on a combination of registered IR images (TI = 150 ms and TI = 1500 ms) on a transverse slice through the base of the genu and splenium of the corpus callosum. For the reproducibility data, TWC and MWF maps were generated for each scan and then registered by applying a registration matrix produced by registering the images from the first echo of each GRASE data set.

2.4. T_2 decay curve analysis

Voxel-wise T_2 distributions were calculated using a modified Extended Phase Graph algorithm combined with regularized nonnegative least squares (NNLS) and flip angle optimization (B_1^+ inhomogeneity correction) [41,42]. Voxel-wise MWF was defined as the sum of the amplitudes with T_2 relaxation times between 15 and 40 ms relative to the total sum of the amplitudes in the T_2 distribution [17].

2.5. Calculation of water content

Tissue water content can be estimated by integrating the T_2 distribution, which gives the signal at time 0 (S_o). S_o is proportional to the equilibrium magnetization (M_o), and therefore the amount of water that is present in the voxel [24,37,38]. The signal of a multi-echo spin-echo sequence, corrected for T_2 decay and B_1^+ (which is the result of the T_2 fitting procedure), is given by:

$$S_o = kB_1^- M_o\left[1-\exp\left(-\frac{TR_{eff}}{T_1}\right)\right]. \quad (1)$$

k is a spatially invariant constant offset which incorporates the receiver gain and scaling parameters. B_1^- is a spatially varying function which reflects the sensitivity of the receiver coil. The portion in square brackets describes the effects of T_1 weighting on signal amplitude, where TR_{eff} is the signal recovery time between the last echo and the next excitation pulse (680 ms).

2.5.1. T_1 correction

Total signal at time 0 was corrected for T_1 relaxation by dividing by the expression ($1-\exp(-TR_{eff}/T_1)$). Because our IR sequence was not optimized for measurement of long T_1's , CSF in the ventricles was corrected with a T_1 of 4.3 s [43], while all other voxels were corrected using the T_1 obtained from the IR data, which was fit with a mono-exponential. CSF was identified using the segmentation method described in Section 2.5.3.

2.5.2. B_1^- correction

T_1 corrected signal maps were divided by a B_1^- map, which was obtained from the body coil sensitivity image. The body coil sensitivity sequence, also known as the "reference scan" on Philips scanners, is a low resolution, low flip angle SPGR sequence with short TR and TE, which is required for all sequences using SENSE or CLEAR reconstruction. The signal equation for an SPGR sequence is given below, where α is the nominal flip angle and B_1^+ is the actual to nominal flip angle ratio, which reflects the transmit inhomogeneity.

$$S = kM_0B_1^-\frac{1-e^{-TR/T_1}}{1-\cos(B_1^+\alpha)e^{-TR/T_1}}\sin(B_1^+\alpha)e^{-TE/T_2^*} \quad (2)$$

For very small flip angles (in this case, 1°), this equation simplifies to.

$$S\cong kM_0B_1^-B_1^+\alpha e^{-TE/T_2^*}. \quad (3)$$

If one assumes that e^{-TE/T_2^*} is spatially invariant for very small TE, that M_o exhibits low image contrast, and that $B_1^+ \approx B_1^-$ (reciprocity of transmit and receive), a B_1^- map can be approximated by taking the square root of the signal in this body coil image and smoothing the result (median filter with a 3 × 3 × 3 voxel kernel). A similar B_1 correction, based on a small flip angle steady state image, has been performed previously [29]. It is important to note that this map will reflect the B_1^- inhomogeneity of the body coil; however, because the GRASE sequence makes use of SENSE, which combines individual receive coil images to match this body coil image, the GRASE images should also reflect the B_1^- inhomogeneity of the body coil. Fig. 1 demonstrates that the correction works quite well in a uniform water phantom, which should