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Original contribution

Effect of echo time and T_2-weighting on GRASE-based T_1w/T_2w ratio measurements at 3T

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ABSTRACT

Tissue contrast can be enhanced by dividing T_1-weighted (T_1w) images by T_2-weighted (T_2w) images to map the so-called T_1w/T_2w ratio, which has become an increasingly popular technique for quantifying brain tissue changes associated with neurodevelopment, aging, and a variety of neurodegenerative diseases. However, although it is self-evident that T_1w/T_2w ratios increase with the amount of T_2-weighting in the T_2w image – which is determined by the echo time (TE), all else being equal – longer TEs also reduce the signal-to-noise ratio (SNR) of the T_2w images, and it is not clear how these SNR characteristics affect the reliability of T_1w/T_2w measurements. Therefore, the current study systematically investigated how different amounts of T_2-weighting affected T_1w/T_2w measurements in order to determine whether there is an optimal amount of T_2-weighting. T_1w images were acquired from 10 neurologically healthy adults using a 3D turbo field echo (TFE) sequence, and a series of T_2-weighted images were extracted from a multi-echo 3D combined gradient- and spin-echo (GRASE) sequence. Analyses of 12 anatomically defined brain regions revealed that both the mean and standard deviation of the T_1w/T_2w measurements increased exponentially with TE of the T_2w images, and that T_2w images with TE ≈ 120–160 ms yielded the most consistent/reproducible contrast between white matter ROIs and the whole-brain T_1w/T_2w signal. Furthermore, comparisons between T_1w/T_2w measurements and multi-component T_2-relaxation myelin water fractions (MWFs) in the same brain regions revealed that T_2w images with TE ≥ 160 ms drastically reduced the degree of correlation between T_1w/T_2w measurements and MWF. Overall, these findings suggest that: 1) there is a substantial trade-off between increased T_1w/T_2w contrast (based on longer TEs for the T_2w images) and the reliability of quantitative T_1w/T_2w signals; and 2) the optimal TE for T_2w GRASE scans is between 120 ms and 160 ms for calculating T_1w/T_2w ratios.

1. Introduction

One of the greatest strengths of MRI stems from the fact that images can be sensitized to different aspects of tissue microstructure, and as a result, there are several contrasts that can be used to non-invasively probe microstructural integrity throughout the brain and spinal cord [1]. Conventional T_1-weighted (T_1w) imaging and T_2-weighted (T_2w) imaging have been widely used in clinical exams due to their sensitivity to pathological processes. For example, T_1w imaging (with or without gadolinium contrast) and T_2w imaging (with or without fluid attenuated inversion recovery; FLAIR) are the most common tools for assessing gray matter (GM) atrophy and white matter (WM) lesions in multiple sclerosis, optic neuritis, neuromyelitis optica and other demyelinating disorders [2–9]. However, although they provide tremendous clinical value, T_1w and T_2w images are often evaluated qualitatively rather than quantitatively [3,5], and their sensitivity and specificity to particular aspects of tissue microstructure is limited [10]. Consequently, there has been great interest in developing 'advanced' MRI approaches that are more sensitive and specific to changes in brain tissue microstructure, including diffusion tensor imaging (DTI) [11,12], high angular resolution diffusion imaging (HARDI) [13], magnetization transfer imaging (MTI) [14], multi-component T_2-relaxation myelin water imaging (MWI) [15], and multi-component driven equilibrium single pulse observation of T_1 and T_2 (mcDESPOT) [16]. However, the acquisition and analyses of such datasets are often time-consuming and technically challenging [see [17,18] for recent reviews], which are

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significant barriers for clinicians and novice researchers.

Recently, however, a novel (albeit simple) approach has been proposed [19], where data from T_1w and T_2w images are combined to assess tissue microstructure via T_1w/T_2w ratio maps. This method was originally proposed as a measure for quantifying intra-cortical myelin content [19–22], but has also recently evolved to include various calibrated approaches and whole brain applications [23–25].

In the T_1w/T_2w method, T_1w images (with high WM signal intensities, relative to GM or cerebrospinal fluid, CSF) are divided by T_2w images (with low WM signal intensities, relative to GM or CSF) in order to increase the amount of tissue contrast and apparent WM signal compared to T_1w or T_2w values in isolation. Similarly, since both myelin content and inflammation/swelling affect T_1w and T_2w signals in opposing directions (with decreased myelin and/or increased tissue swelling commonly observed as T_1-hypointense and T_2-hyperintense brain lesions), it is thought that whole-brain T_1w/T_2w ratio maps could provide a sensitive (and potentially quantitative) measure that is related to myelination and microstructural integrity of WM and other subcortical structures among neonates [26], multiple sclerosis patients [23,27], schizophrenia patients [28,29], bipolar disorder patients [30], and that it might also serve as a biomarker for amyloid beta [31].

Indeed, the T_1w/T_2w approach has several features that make it attractive for both research and clinical applications. First, it does not rely on high magnetic field strength and conventional T_1w and T_2w pulse sequences are ubiquitous, so data can be acquired on practically any MRI system. Second, the required scan times are relatively short and T_1w and T_2w images are almost always collected for other clinical or research purposes, so in most cases overall scan/experiment times need not be increased. Third, the image post-processing is relatively fast and simple compared to other quantitative WM imaging methods (e.g., diffusion or myelin water imaging approaches), and the resulting maps can be used for either subjective clinical evaluations or more detailed quantitative analyses. Fourth, although comparisons with gold-standard MWI methods have shown that T_1w/T_2w ratios are not specific to myelin concentration in subcortical structures [32,33], test-retest studies have demonstrated that T_1w/T_2w measurements are very repeatable/reliable [32] as a general measure of tissue microstructure. Finally, and partially to address concerns about specificity to myelin concentration, our group has recently shown that a multi-echo 3D GRASE sequence can be used instead of fast spin echo (FSE) or other sequences for T_2w image acquisition in order to calculate T_1w/T_2w ratios – thereby allowing whole-brain T_1w/T_2w mapping and MWI based on the same T_2w data [33].

However, several previous studies have calculated T_1w/T_2w ratios using T_2w images with different echo times – using either conventional FSE sequences [23,25,26,28,29,31] or stimulated echo sequences such as sampling perfection with application-optimized contrast with different flip-angle evolutions (SPACE) [19,21,24,32]. For conventional FSE sequences, T_1w/T_2w ratios have been calculated using T_2w images with TE = 68 ms [29], 80 ms [25,26,28], 100 ms [25]; 101 ms [31,33], 140 ms [23]. Nonetheless, although T_1w/T_2w values will depend on the degree of T_1- and T_2-weighting in the composite images, to the best of our knowledge, no previous studies have systematically examined how these parameters affect the resulting T_1w/T_2w ratio maps – especially in regard to multi-echo GRASE data [33], where images are produced with increasing amounts of T_2-weighting. Therefore, the goals of the current study were to: 1) acquire a "standard" T_1w image and a series of T_2w images with different echo times in order to empirically determine how the amount of T_2-weighting affects T_1w/T_2w ratios; and 2) determine the optimal T_2-weighting (or range of T_2-weightings) for calculating GRASE-based T_1w/T_2w ratios in subcortical brain structures.

2. Methods

2.1. Study participants

Ten neurologically healthy volunteers (5 male; 5 female) were recruited from the Charles Village and Roland Park communities in Baltimore, Maryland, USA. The study was approved by the Johns Hopkins University Institutional Review Board, and all volunteers provided written informed consent prior to enrollment. Participants were verbally screened to ensure that none had a history of neurological injury/disease, psychiatric illness, or substance abuse (including alcohol or tobacco), and all T_1w images were reviewed by a board-certified radiologist to confirm the absence of structural abnormalities or other incidental pathological findings. The age of participants spanned a relatively broad range (males 27.0 ± 6.6 years; females 29.0 ± 10.9 years),and were not significantly different between males and females ($p = 0.74$).

2.2. Data acquisition

Neuroimaging data were acquired using a whole-body 3 T Philips Achieva MRI system equipped with a 32-channel SENSE head coil (*Philips Healthcare*, *Best*, *The Netherlands*). High-resolution T_1-weighted images were acquired using a 3D Turbo Field Echo (TFE) sequence: Inversion Time [TI] = 700.31 ms; Repetition Time [TR] = 7.93 ms; Echo Time [TE] = 3.66 ms; Flip Angle = 8°; SENSE Factor = 2.4; Field Of View [FOV] = 212 mm × 172 mm × 150 mm; Spatial Resolution = 1.00 mm × 1.00 mm × 1.00 mm; Scan Duration = 4.26 min.

Images with varying degrees of T_2-weighting were then acquired using a previously reported [15] whole-brain, multi-echo, 3D combined gradient and spin echo (GRASE) sequence: TR = 1500 ms; Echo Train Length [ETL] = 32; Echo Spacing [ESP] = 10 ms; First Echo Time [TE1] = 10 ms; Flip Angles = 90° (excitation) and 180° (refocusing); EPI Factor = 3; SENSE Factor = 4.0; FOV = 212 mm × 212 mm × 96 mm; Spatial Resolution = 0.95 mm × 0.95 mm × 3.00 mm; Scan Duration = 7.29 min.

2.3. Image processing

Data analyses were performed using a combination of image processing software packages, including: SPM8 (*http://www.fil.ion.ucl.ac.uk/spm/software/spm8/*, *Wellcome Trust Centre for Neuroimaging*, *London*, *UK*), MRIStudio (*https://www.mristudio.org/*, *Johns Hopkins University School of Medicine*, *Baltimore*, *Maryland*, *USA*), and custom MATLAB scripts.

Before any statistical analyses, T_1w and T_2w images went through a comprehensive preprocessing pipeline (Fig. 1). For each participant, the 3D GRASE images (i.e., T_2w images acquired with different echo times) were coregistered with the T_1w image and resliced to 1 mm^3 resolution using the "resize_img.m" script (*http://www0.cs.ucl.ac.uk/staff/G.Ridgway/vbm/resize_img.m*, *University College London*, *UK*). Skull stripping was then performed using a previously-reported two-step procedure [34], in which the "New Segment Tool" in SPM8 was used to create a brain mask from the resliced T_1w image, and these images were then manually refined to remove any remaining skull/scalp using the ROIEditor toolbox in MRIStudio. The coregistered and skull-stripped T_1w anatomical images for each participant were then spatially normalized to the "*JHU_MNI_SS_T1_ss*" template [35] in Montreal Neurological Institute (MNI) space [36]. This was implemented using the DiffeoMap toolbox in MRIStudio to carry out a 12-parameter affine (linear) transformation, followed by high-dimensional, non-linear warping based on the large deformation diffeomorphic metric mapping (LDDMM) algorithm [37] with cascading elasticity (i.e., $\alpha = 0.01$, $\alpha = 0.005$, and $\alpha = 0.002$) to allow increasingly nonlinear deformations. The T_1w and T_2w images for each volunteer were then warped to