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Myelin water and T_2 relaxation measurements in the healthy cervical spinal cord at 3.0T: Repeatability and changes with age

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ABSTRACT

Multiecho T_2 relaxation measurements offer specific information about myelin content through the myelin water fraction (MWF), as well as about the water environments through the intra- and extra-cellular (IE), and global, geometric mean T_2 (GMT_2) times. While these measurements have yielded new insights into brain development and pathologies, they have yet to be thoroughly investigated in the spinal cord. The goals of this study were: (1) to apply a new 3D multiecho T_2 relaxation measurement in the cervical spine with sufficient axial resolution to distinguish grey and white matter; (2) to perform a pilot reliability assessment of the resulting MWF and GMT_2 measures in a target population; and (3) to detect differences in these measures between a younger cohort (20–30 years of age) and an older cohort (50–75 years of age) of healthy adults. The results demonstrated that the MWF in younger healthy adults follows the known pattern of lower myelin content in grey matter (mean (95% confidence interval)) (0.049 (0.030–0.067)) as compared to white matter (0.296 (0.275–0.317), $p<0.001$). The reliability coefficients were 0.65 and 0.82 for the MWF in the dorsal (DC) and lateral column (LC) white matter, respectively; 0.79 and 0.52 for the IE GMT_2; and 0.74 and 0.73 for the global GMT_2. Significantly lower MWF were found in the older adults than in the younger adults (DC $p=0.014$; LC $p=0.012$), as well as lower IE GMT_2 times (DC $p=0.008$; LC $p=0.042$), however, the global GMT_2 times did not show any differences. These changes in MWF and IE GMT_2 times, but not in global GMT_2 times, indicate that multiecho T_2 relaxation measures are sensitive to changes in myelin integrity and cell morphology that may not be apparent on conventional T_2 weighted images.

Introduction

Myelin water imaging is a magnetic resonance imaging (MRI) technique that exploits the different transverse relaxation rates of water in the various microenvironments of central nervous system tissue to reveal new information not available with conventional imaging strategies. *In vivo* longitudinal (T_1) and transverse (T_2) relaxation experiments in the human brain suggest that tissue water diffuses fast enough compared to the T_1 time to sample all microenvironments and experience an average T_1 time, but slow enough on the T_2 timescale to sample only one environment, allowing water trapped between myelin bilayers to experience a different T_2 time from the intra- and extra-cellular water (Whittall et al., 1997). The fraction of water trapped between myelin bilayers relative to the total tissue water content, termed the myelin water fraction (MWF), can be thus be extracted as a surrogate marker for myelin content.

The ability of the MWF to provide a surrogate marker for myelin content has previously been demonstrated via *ex vivo* MRI and histological studies (Laule et al., 2006, 2008), and the MWF has been used to measure changes in myelin content in patients suffering from multiple sclerosis (MS) (Laule et al., 2004a; Moore et al., 2008; Vavasour et al., 2009), phenylketonuria (Sirrs et al., 2007; Vermathen et al., 2007), and schizophrenia (Flynn et al., 2003), as well as to track myelination during brain development (Whitaker et al., 2008). While myelin water imaging has been used to investigate clinical questions about brain myelin content, progress in the application to the spinal cord (SC) has lagged behind. Recently, myelin water content has been measured in rats with induced cervical spinal cord injury (Kozlowski et al., 2008), in healthy humans (Minty et al., 2009; Wu et al., 2006), and in patients with MS (Laule et al., 2004b; Wu et al., 2006); however the human studies were limited to a single-slice acquisition, and suffered from the inability to distinguish between grey and white

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matter (GM, and WM, respectively). These limitations may be overcome thanks to recent advancements in multiple echo and 3D acquisitions (Mädler et al., 2008; Oh et al., 2007) which enable myelin water imaging to cover a longer extent of the cord within the same time period and with improved axial resolution. Myelin water imaging in the brain using a new multiecho sequence shows a distinct difference in MWF between GM and WM (Mädler et al., 2008), and there should likewise be a measurable difference in the SC. Finally, while frontal brain WM MWF was found to increase with age from 15 to 55 years (Flynn et al., 2003), a similar study of age-related MWF changes has yet to be conducted in the spinal cord. A post-mortem histology study of degenerative changes of the corticospinal tract concluded that small myelinated fibre density strongly decreases in the cervical spinal cord with age from 19 to 90 years (Terao et al., 1994), and thus it is expected that SC MWF will similarly be reduced with increasing age.

The purpose of the present study was to apply a new 3D multiecho T_2 relaxation pulse sequence (Mädler et al., 2008) to the cervical spinal cord in normal healthy controls with the aims to characterize the distribution of MWF in GM and WM in younger adults, perform a pilot scan–rescan repeatability assessment in a healthy target population for cervical spondylotic myelopathy, and determine whether there is a reduction in the MWF of older adults. Additionally, 32 echo measurements offer more information about the T_2 distribution than just the MWF, and measures such as the geometric mean T_2 times have yet to be reported in SC white and grey matter.

Methods

Subject information

Twelve healthy young adults aged 21 through 30 (7 female, 5 male, mean age 25 years) were initially recruited, and 18 healthy older adults aged 51 through 75 (11 female, 7 male, mean age 61 years), were recruited in a second phase one year later. Written informed consent was obtained with approval from the Clinical Research Ethics Board of our institution.

Magnetic resonance experiment

MRI scans were performed with a phased array spine coil, using only the first 4 elements for best localization of the cervical SC, on a Philips 3.0T Achieva system (Philips Medical Systems, Best, The Netherlands). All subjects were scanned with localizer and sagittal T_2 weighted imaging (T_2WI) sequences to orient axial slices perpendicular to the SC as shown in Fig. 1a; an additional axial higher in-plane resolution (0.45 mm × 0.45 mm) T_2WI sequence was acquired from the over 50 years cohort for improved GM and WM contrast, as shown in Fig. 1c. T_2 measurement of the cervical cord was performed in all subjects via the acquisition of a 3D 32 echo sequence (Mädler et al., 2008). The 3D volume was centered at the C5 vertebral body, however, in some subjects the volume was centered more cranially to avoid phase-wrap artifact from the shoulders since the fold-over direction had been chosen as right-left to avoid artifacts from swallowing motion. The multiecho sequence was acquired with a single acquisition, a field of view (FOV) = 180 mm × 135 mm × 40 mm with matrix size 259 × 96, and reconstructed into 8 axial slices, each 5mm thick with an in-plane resolution of 0.7 mm × 0.7 mm. The first echo began 10ms after a slice-selective 90° pulse, followed by 31 echoes arising from composite block (90°x–180°y–90°x) refocusing pulses featuring a series of slice-selective crusher gradient pulses of alternating sign and descending amplitude on either side of each refocusing pulse to eliminate contributions from stimulated echoes. The TR was 1300 ms, yielding a total scan time of 20 min. Saturation bands could not be used to suppress signal from outside the spinal cord due to off-resonance excitation of non-aqueous protons within the cord that would then exchange magnetization with the aqueous protons. Scan–rescan repeatability was tested in eight subjects of the over 50 years cohort by acquiring a second MRI scan within one week.

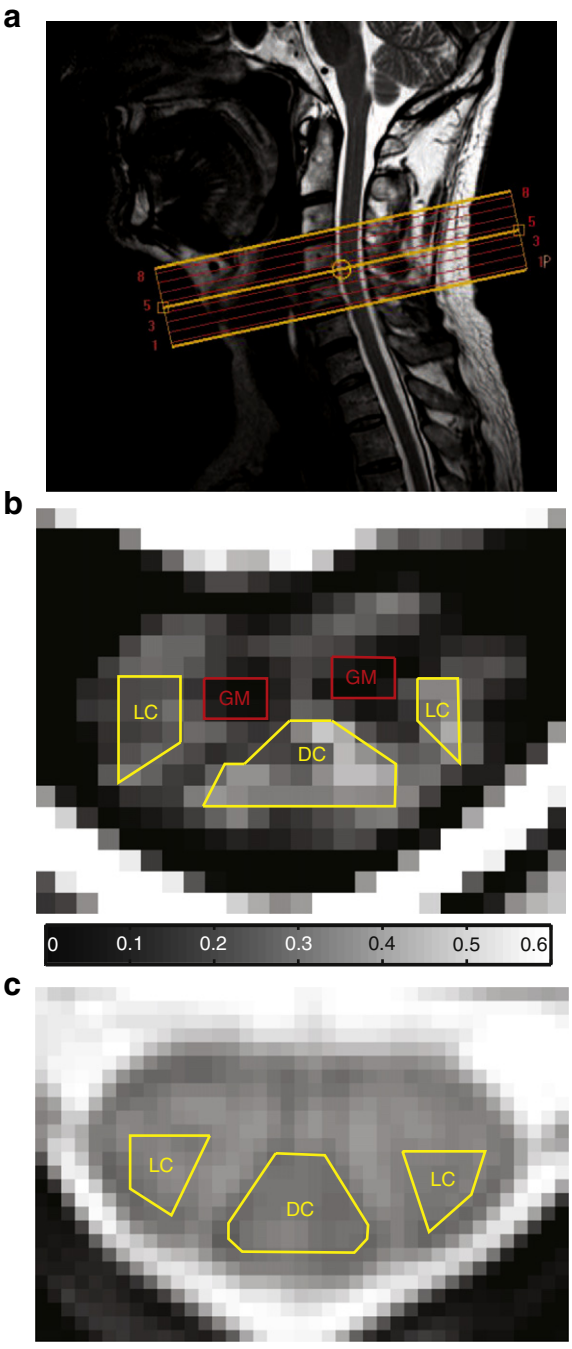

Fig. 1. Location of 3D multiecho stack and placement of ROIs. a) Alignment of multiecho stack of slices centered on the C4/C5 intervertebral disc level on a sagittal T_2WI. b) Location of grey and white matter ROIs on a MWF map of a young healthy adult with MWF scale directly below. c) Location of white matter ROIs on axial T_2WI of an older healthy adult.

Magnetic resonance data analysis

The 32 echo decay curve was fit on a voxel by voxel basis (Meyers et al., 2009) using a regularized non-negative least squares (NNLS) algorithm (in-house software) with 120 input relaxation times logarithmically spaced from 15 ms to 2 s, and no *a priori* assumptions about the number of exponential components that must be included in the fit (Whittall and MacKay, 1989). There were four parameters of