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Title: Regional T_1 mapping of the whole cervical spinal cord using an optimized MP2RAGE sequence

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Abstract

While T_1 measurements present multiple challenges (robustness, acquisition time), the recently-proposed MP2RAGE sequence (Magnetization Prepared 2 Rapid Acquisition Gradient Echoes) has opened new perspectives to characterize tissue microstructure changes occurring in pathological or developmental context. Extensively used for brain studies, it was herein adapted to investigate the cervical spinal cord (SC) at 3T.

By integrating Bloch equations, the MP2RAGE sequence parameters were chosen to optimize SC gray matter / white matter (GM/WM) T_1 contrast with sub-millimetric resolution, a scan time <10 min, a reliable T_1 determination with minimal B_1^+ variation effect, within a range of values compatible with different pathologies and surrounding structures. The residual B_1^+-effect on T_1 values was corrected using a look-up-table approach and B_1^+ mapping. The accuracy of B_1^+-corrected T_1 measurements was assessed on phantom with respect to conventional inversion-recovery (IR). In vivo MP2RAGE acquisitions were performed on five young (28.8±4.3yo) and five elderly (60.2±2.9yo) volunteers and analyzed using a template-based approach.

Phantom experiments led to high agreements between IR-SE and MP2RAGE-based T_1 values (R^2=0.997). In vivo T_1 values for cervical WM, anterior GM, posterior sensory (PST) and lateral motor tracts (LMT) were: 917±29ms, 934±33ms, 920±37ms and 877±35ms, respectively, all subjects and cervical levels considered. Significant differences were observed between anterior GM and LMT, and between LMT and PST, in agreement with the literature. Repeated T_1 measurements demonstrated high reproducibility of the MP2RAGE in the SC (variation coefficient < 5% in all regions of interest). Finally, preliminary assessment of age-related SC tissue microstructure variation additionally showed evidences of SC atrophy and slight trends of T_1 decrease with age in all regions.

Overall, this study shows that fast, robust and accurate sub-millimetric resolution T_1-mapping in the cervical SC using the MP2RAGE sequence is possible, paving the way for future multi-centric and longitudinal clinical studies investigating the pathological cord.

Keywords

- Spinal cord;
- T_1 mapping;
- MP2RAGE;
- Relaxometry;
- White matter;
- Gray matter;
- Spinal cord template.

Abbreviations

(a)GM	*(anterior) Gray matter*
ANOVA	*Analysis of variance*
COV	*Coefficient of variation*
CSA	*Cross-sectional area*
CSF	*Cerebrospinal Fluid*
EPI	*Echo Planar Imaging*
FLASH	*Fast low-angle shot*
FOV	*Field of view*
GRE	*Gradient Echo*
IR-SE	*Inversion-Recovery Spin-Echo*
LUT	*Look-up-table*
MP2RAGE	*Magnetization Prepared 2 Rapid Acquisition Gradient Echoes*
MR(I)	*Magnetic Resonance (Imaging)*
PVE	*Partial volume effect*
RF	*Radiofrequency*
RMSE	*Root Mean square error*
ROI	*Region of Interest*
SC	*Spinal Cord*
STD	*Standard deviation*
VFA	*Variable Flip Angle*
WM	*White Matter*

Highlights

- Fast and sub-millimetric T_1 mapping of the entire cervical spinal cord at 3T.
- Efficient and robust B_1^+ inhomogeneity correction using B_1^+ mapping and look-up-table approach.
- Accurate and reproducible T_1 quantification of spinal cord GM and postero-lateral WM sub-regions.
- Preliminary age- and tract-related T_1 variations in the cervical spinal cord.
- Feasibility of morphological measurements on MP2RAGE T_1 map.

1. Introduction

Quantitative mapping of Magnetic Resonance (MR) longitudinal relaxation time, referred to as T_1 relaxometry, is not only important for the determination of adequate MR sequence parameters, it also offers tremendous perspectives for structural and pathological tissue characterization in different organs[1,2]. The T_1 relaxation time, or spin-lattice relaxation time, is indeed tissue- and field-specific, and a growing amount of work supports the use of T_1-mapping as an *in vivo* marker of tissue microstructure in clinical and neuroscientific research, probing for instance disease-related tissue changes[3–5] or developmental plasticity and ageing[6–8].

Over the years, numerous MR techniques have been proposed and used to estimate T_1 values[9]. These include saturation-recovery[10] and inversion-recovery (IR)[11] based measurements, Look-Locker[12] techniques and faster methods based on variable flip angles (VFA), such as the VFA ultrashort echo time[13] and the Driven Equilibrium Single Pulse Observation of T_1 (DESPOT1) method[14]. The gold standard method for T_1-mapping remains the inversion-recovery spin-echo (IR-SE) technique using multiple inversion times (TIs). However, IR-SE acquisition times are prohibiting and hence not suitable for clinical routine. Consequently, many efforts have been made to shorten the T_1 mapping acquisition times. In this context, the modified Look-Locker (MOLLI) methods[15], a common variation of the IR technique with multiple RF pulses applied during the longitudinal recovery to allow for curve-fitting T_1 estimation in a relatively short scan time, are well-established T_1-mapping techniques, particularly suited for cardiac MRI. Another highly popular alternative for rapid T_1 relaxometry in the brain, although affected by imperfect RF spoiling and B_1^+ variations, is the DESPOT1 method[14], based on VFA and combined with 3D or 2D spoiled Gradient-Recalled Echo (GRE) acquisitions.

More recently, there has been a growing interest towards the MP2RAGE (Magnetization Prepared 2 Rapid Acquisition Gradient Echoes) sequence[16], an extension of the magnetization-prepared rapid gradient-echo (MPRAGE) sequence[17]. This new sequence provides not only a 3D T_1-weighted volume suitable for morphological analyses whose contrast can be similar to the commonly-used MPRAGE, but also a so-called “uniform” T_1-weighted volume and a corresponding T_1 map. Although already largely used for brain imaging[16,18–22], to the best of our knowledge, quantitative T_1-mapping using MP2RAGE acquisitions in the cervical spinal cord (SC) have only been reported at 7T[23] but never at lower field (3T), where most clinical research studies are performed. As a matter of fact, T_1-

mapping of the cervical SC at 3T reported so far relied either on VFA-based techniques[24–26] or on IR-based approach combined or not with echo-planar imaging (EPI) readout so as to shorten the acquisition time[26,27].

In this study, our goal was to generate both 3D anatomical T_1-weighted images and reliable T_1-mapping of the whole cervical cord by using the MP2RAGE sequence, while ensuring clinically compatible scan time (T_{acq} less than 10 minutes) and sub-millimetric resolution. To do so, MP2RAGE sequence parameters were optimized using Bloch equations to render an optimal contrast between SC gray matter (GM) and white matter (WM) at 3T. The accuracy of the proposed protocol was first assessed using a dedicated T_1-phantom by comparing the MP2RAGE-based T_1 values ($T_1^{MP2RAGE}$) to gold standard IR-SE-based T_1 values (T_1^{IRSE}). The resulting MP2RAGE protocol was then applied *in vivo* for cervical SC explorations. Measurements reproducibility was evaluated through scan-rescan experiments. The obtained T_1 values were also compared to SC T_1 values previously reported in the literature at 3T[24–28]. Finally, given that the knowledge of T_1 values could also help characterizing age- and tract-related structural tissue changes[29,30], a preliminary MP2RAGE-based cervical SC investigation on two age-groups and different regions-of-interest (ROIs) was carried out. In addition, morphological measurements were performed to evaluate possible age-related changes on both the T_1-weighted GRE_{TI2} volume and the $T_1^{MP2RAGE}$ map.

2. Methods

Experiments were performed on a whole body 3T system (MAGNETOM Verio, Siemens Healthcare, Erlangen, Germany), using the body coil for RF transmission and the standard 12-channel head, 4-channel neck and 24-channel spine matrix array coils for signal reception.

2.1. Background

The MP2RAGE sequence[16] can be briefly described as an inversion recovery-based sequence in which two 3D GRE volumes are acquired during the recovery period at two different inversion times (TI_1 and TI_2) with two different flip angles (α_1 and α_2). By combining these two GRE volumes acquired with identical sequence parameters except for the flip angles and inversion times, a composite volume with a so-called “uniform” T_1-weighted contrast ($MP2RAGE_{UNI}$) can be generated with no volume co-registration needed, according to:

$$MP2RAGE_{UNI} = Real\left(\frac{GRE^{*}_{TI1} GRE_{TI2}}{|GRE_{TI1}|^2 + |GRE_{TI2}|^2}\right) \qquad \text{(Eq.1)}$$

where GRE_{TI1} and GRE_{TI2} are the complex signal intensities of the volumes acquired at TI_1 and TI_2 and * the complex conjugate operator; for further details see Appendix 1 of Marques et al.[16]. According to Eq. (1), the $MP2RAGE_{UNI}$ volume signal is limited within the [-0.5; +0.5] range and is to a large extent purely T_1-weighted, i.e. with almost no proton density, T_2* and B_1^- dependences[16]. Consequently, this volume provides an excellent basis for T_1 estimation using Bloch-based signal simulations. Indeed, a Look-Up-Table (LUT) can be constructed by using the analytical signal model reported in[16] and used to estimate the T_1 value of each pixel.

However, since homogeneous flip angle prescription through the imaged volume may be hard to achieve due to transmit field (B_1^+) inhomogeneities, especially above 1.5T or if large volumes are excited as it is the case in SC acquisitions at 3T, the $MP2RAGE_{UNI}$ signal may suffer from B_1^+ bias and thus lead to inaccurate T_1 estimation depending on the amplitude of the flip angle deviation. To alleviate this potential B_1^+ bias, the MP2RAGE prescribed flip angle values could be decreased, but at the expense of a contrast-to-noise ratio reduction[16]. Alternatively, another approach relying on additional B_1^+ mapping acquisition combined with a set of LUT accounting for B_1^+ variations (i.e. a 3D LUT) could be used during post-processing[18,23]. In this study, a careful attention was directed toward the optimization of the flip angles (α_1 and α_2) in order to limit B_1^+ variation effects on T_1 measurements. Additionally, B_1^+ maps were acquired to further correct T_1 values from potential residual B_1^+ variation effects.

2.2. <u>Sequence parameters optimization</u>

The first requirement for this study was to find the MP2RAGE sequence parameters that provide an optimal SC GM/WM T_1 contrast (defined here as $MP2RAGE_{UNI}$ signal intensity difference) at 3T. To do so, the T_1 values reported by[26] for SC GM and WM (973±33 ms and 876±27 ms, respectively) were used as a starting point to perform iterative Bloch simulations. A subset of sequence parameters was additionally fixed to ensure a total scanning time under 8 min, a large spatial coverage including the whole cervical cord and a sub-millimetric spatial resolution (<1 mm^3). Hence:

- The repetition times of the sequence ($MP2RAGE_{TR}$) and the GRE modules (GRE_{TR}) were set to 4 s and 6 ms, respectively.

- A sagittal field of view (FOV) covering both brain and whole cervical spine and placed at the isocenter was used (FOV: 243x300 mm², number of excitations per GRE module (GRE_n): 176, phase/slice partial Fourier (PF) factor: 6/8; slice thickness: 1 mm), with an in-plane resolution of 0.9x0.9 mm^2.

The other sequence parameters (flip angles and inversion times) were investigated as follows:

- TI_1 and TI_2 were varied from (GRE_n*PF*GRE_{TR}/2) to $MP2RAGE_{TR}$-(GRE_n*PF*GRE_{TR}/2) in steps of 50 ms while keeping the condition TI_2-TI_1>(GRE_n*PF*GRE_{TR}) true.
- The flip angles of the two GRE modules (α_1 and α_2) were independently varied from 1 to 15 degrees, by 1-degree steps.

Bloch simulations were performed using Matlab (MATLAB R2014a, MathWorks, Natick, MA, USA) for all possible combinations of TI_1, TI_2, α_1 and α_2. Optimal sequence parameters were chosen so that:

- the difference between $MP2RAGE_{UNI}$ signal values in SC GM and WM was maximum, and
- the relationship between the $MP2RAGE_{UNI}$ signal and T_1 values was bijective for the [500 ms – 3000 ms] T_1 value range, which was motivated by pathological T_1 values found in the literature (ranging from 1200±400 ms to 1500±200 ms in multiple sclerosis (MS) lesions [5]) while also considering the surrounding cerebrospinal fluid and intervertebral disk T_1 values at 3T (in the order of 2500ms[16], 1140±76 ms (*nucleus pulposus*) and 706±44 ms (*annulus fibrosus*)[31], respectively).

Although the main objective of the study was not to provide a MP2RAGE sequence immune from B_1^+ inhomogeneities, the choice of the MR parameters was nonetheless aimed to find a minimal influence on $MP2RAGE_{UNI}$ signal and $T_1^{MP2RAGE}$ values within the range of T_1 of interest. This would allow for simpler and shorter post-processing if one does not need to perform the B_1^+ correction.

2.3. T_1 measurements and B_1^+ correction validation on phantom

To validate the accuracy of $T_1^{MP2RAGE}$ measurements with the chosen MR parameters, a phantom (Eurospin II test objects, Diagnostic Sonar, Livingston, Scotland) containing 12 different tubes filled with gadolinium-doped agar gel with theoretical T_1 values mimicking

those expected in the healthy and pathological SC and ranging between 500 ms and 1700 ms was used (see *Fig. 3b*).

The optimized MP2RAGE protocol was therefore run with the following parameters (TR 4 s; TE: 2.48 ms; GRAPPA: 2, α_1/α_2: 4/5°, TI_1/TI_2: 650/2000 ms, TR-FOCI inversion pulse[32], FOV: 243x300 mm² placed at the isocenter, GRE_n: 176, phase/slice PF factor: 6/8; voxel size of 0.9x0.9x1 mm^3, standard B_0 shimming). To correct for potential residual B_1^+ inhomogeneity effects on $MP2RAGE_{UNI}$ image and $T_1^{MP2RAGE}$ map (see paragraph 2.5 for correction method details), a sagittal 2D magnetization-prepared turbo-FLASH B_1^+-mapping[33] sequence was additionally acquired (TR: 5 s; TE: 3.42 ms; slice thickness: 5 mm; FOV: 250x250 mm; matrix size: 320x320; voxel size 1.5x1.5mm^2; preparation flip angle: 45°, sinc shape, T_{acq}: 1 min).

As a reference, the phantom was also scanned using a conventional single-slice inversion-recovery spin-echo (IR-SE) sequence with nine different inversion times (TR: 9 s; TI: [0.1/0.2/0.4/0.5/0.7/0.8/0.9/1.1/1.3 s]; slice thickness: 2 mm; FOV: 256 mm; matrix size: 128; T_{acq} ~20 min per TI). Afterwards, T_1^{IRSE} values were calculated on a pixel-wise basis using a mono-exponential fit of the signal recovery curve, computed on Matlab.
For quantitative analysis, twelve regions of interest were drawn on the T_1^{IRSE} map, then the B_1^+-corrected $T_1^{MP2RAGE}$ and B_1^+ maps were resliced to the T_1^{IRSE} map using c3D (linear interpolation) (c3D, ITK-SNAP, University of Pennsylvania, PA, USA) so that the same twelve ROIs could be used to extract their mean and standard deviation values per tube. $T_1^{MP2RAGE}$ and T_1^{IRSE} reproducibility was evaluated by repeating the whole experiment at three different timepoints.

To evaluate the efficiency of the custom B_1^+-correction method on $T_1^{MP2RAGE}$ measurements, 6 MP2RAGE acquisitions were performed while varying the reference voltage from 70% to 120% of its nominal value, in steps of 10%. These values were chosen so as to cover the minimal and maximal variations (69% and 119%, respectively) observed *in vivo* (see *Fig. 6*) in the cervical spinal cord using our system. For each tube, mean and standard deviation $T_1^{MP2RAGE}$ values from all 6 MP2RAGE acquisitions were computed before and after B_1^+ correction. To evaluate the efficacy of the B_1^+ correction, the Root Mean Squared Error (RMSE) was evaluated for each tube and each acquisition and an averaged RMSE value across all tubes from all 6 acquisitions was subsequently computed.

2.4. ***In vivo* T_1 relaxometry**

As a preliminary application of the SC-dedicated MP2RAGE sequence, data from ten healthy volunteers (5 young subjects, 28.8±4.3 years old; 5 elderly subjects, 60.2±2.9 years old) were acquired to assess ~~age and~~ tract-related structural changes in cervical SC tissues. The protocol was approved by the local institutional ethics review board and written informed consent from all subjects was obtained before participation. The 3D MP2RAGE sequence covering the whole brain and the SC from C_1 to C_7 was acquired using the previously chosen parameters and the same main parameters than used for the phantom experiment described above. Acquisition time was 7:18 min.

Similarly, the 2D sagittal magnetization-prepared turbo-FLASH B_1^+ mapping sequence[33] covering the cervical SC (TR: 5 s; TE: 3.42 ms; slice thickness: 5 mm; FOV: 250x250 mm; matrix size: 320x320; preparation flip angle: 45°, sinc shape, 3 slices, voxel size 1.5x1.5mm^2, T_{acq}: 1 min) was acquired for B_1^+-correction of $T_1^{MP2RAGE}$ maps.

Three subjects were explored at three different time points for reproducibility assessment.

2.5. Image processing

The first step of the data post-processing was to build the LUT linking the $MP2RAGE_{UNI}$ signal intensities to T_1 values[16]. The LUT was built under Matlab for different values of T_1 ranging from 0.1 to 3.5 s with steps of 10 ms and for relative B_1^+ variation (flip angle variation) ranging from 50% to 150% of the nominal reference value (100%/45°). The 3D LUT was then used to generate the corrected $T_1^{MP2RAGE}$ map based on the B_1^+-map and the $MP2RAGE_{UNI}$ reconstructed by the scanner based on the acquired GRE_{TI1} and GRE_{TI2} volumes. Finally, a denoising step was performed on the reconstructed $T_1^{MP2RAGE}$ map using BM4D[34] for better visualisation.

The subsequent *in vivo* ROI-based T_1 quantification largely relied on the Spinal Cord Toolbox[35] and dedicated SC templates (MNI-Poly-AMU[36], AMU_{40}[37], WM pathways[38]), allowing for automatic regional $T_1^{MP2RAGE}$ quantification at all cervical levels from C_1 to C_7, as described in Massire et al.[23]. Automated GM/WM segmentation and WM tracts delineation in the common reference template space were obtained after the binarization (threshold: 0.5) of the probabilistic GM/WM AMU_{40} and WM pathways atlases, respectively. $T_1^{MP2RAGE}$ values were then extracted from anterior GM horns (aGM), lateral motor (corticospinal and rubrospinal) tracts (LMT), posterior sensory (gracile and cuneate) tracts (PST) and whole WM for all slices. Average values per cervical level from C_1 to C_7 were computed. Total GM

ROI was not considered for T_1 evaluation due to potential partial volume effects (PVE) in the dorsal horns.

Cord cross-sectional areas (CSA) were extracted using automatic cord segmentation (PropSeg[35]) on both anatomical T_1-weighted GRE_{TI2} (with MPRAGE-like contrast) and $T_1^{MP2RAGE}$ map in the subject space to demonstrate the CSA measurement feasibility on the $T_1^{MP2RAGE}$ map. Slice-by-slice and average values per cervical level from C_1 to C_7 were computed. Compliance between CSA values from GRE_{TI2} and $T_1^{MP2RAGE}$ map was evaluated and preliminary evaluation of age-related morphological changes was conducted.

2.6. Statistical analyses

All statistical analyses were performed using JMP9 (SAS institute, Cary, NC, USA), considering *p*-values less than 0.05 for statistical significance.

Correlation between B_1^+-corrected $T_1^{MP2RAGE}$ and T_1^{IRSE} values was assessed using linear regression and Bland-Altman plot was performed for further evaluation of measurement bias. To assess the *in vitro* reproducibility of the T_1 measurement methods, T_1^{IRSE} and B_1^+-corrected $T_1^{MP2RAGE}$ coefficient of variations (COV, in %) were computed as $COV=100.\rho/\mu$, where μ is the inter-scan mean and ρ the standard deviation for the T_1 measurements in each tube of the phantom over three time points. Then, global COV for each technique was computed by averaging all COV. *In vivo* reproducibility of the B_1^+-corrected $T_1^{MP2RAGE}$ measurements was also evaluated by quantifying the COV per ROI (aGM, LMT, PST and whole WM) at each cervical level of the 3 participants over three time points. Then, global COV per ROI was computed by averaging values from all three subjects at all levels.

To assess $T_1^{MP2RAGE}$ sensitivity to age- and tract-related structural changes, $T_1^{MP2RAGE}$ values were analyzed using a multi-factorial analysis of variance (ANOVA) testing the effect of age group, ROIs and cervical levels followed by Steel-Dwass all pairs tests when the effects were significant. Bonferroni correction for multiple comparisons were performed when needed.

Correlation between GRE_{TI2} and $T_1^{MP2RAGE}$-based slice-by-slice CSA measurements was evaluated using linear regression and Bland-Altman plot. Preliminary evaluation of age-related morphological changes was performed using Wilcoxon rank tests on CSA values from the two age-groups at each cervical level, corrected for multiple comparisons.

3. Results

3.1. Sequence parameters optimization and phantom validation

Fig. 1 presents the results of the $MP2RAGE_{UNI}$ GM/WM contrast optimization as a function of α_1, α_2, TI_1 and TI_2. *Fig. 2* shows the simulated $MP2RAGE_{UNI}$-T_1 relationship for the protocol with optimal parameters (protocol #1) resulting from parameter optimization and the protocol with the chosen parameters (protocol #2), along with the B_1^+-variation effect on each protocol.

As seen on *Fig. 1a*, the maximal GM/WM contrast achievable while ensuring the constraints mentioned in paragraph 2.2 was 0.08, obtained with α_1/α_2=8°/5° and TI_1/TI_2= 650 ms/2000 ms (Protocol #1), which led to a flatter $MP2RAGE_{UNI}$ signal curve than with Protocol#2 (*Fig. 2a*). However, when introducing B_1^+ variation into the Bloch simulations (see *Fig. 2b*), this parameter set led to a high dependence on B_1^+ inhomogeneities (±6% of T_1 values for B_1^+ variations within [70%-120%] range) and a non-bijective $MP2RAGE_{UNI}$-T_1 relationship for a relative B_1^+ value of 70% (typically observed at lower cervical levels) that would affect $T_1^{MP2RAGE}$ measurements in CSF (T_{1CSF} ~2500ms) or in pathological tissue (T_{1MS_lesion} ~1200 to 1700 ms[5]).

The optimum protocol limiting this B_1^+ variation effect while providing reasonable WM/GM signal difference (0.06) was obtained with α_1/α_2=4°/5° and TI_1/TI_2 = 650 ms/2000 ms (Protocol #2, *Fig. 2.c* and *2.d*). The consecutive error on the T_1 estimation due to B_1^+ variations within [70% to 120%] range corresponds to ±3% of the T_1 values (±30 ms and ±20 ms in the GM and WM, respectively) for this protocol. For example, a SC GM voxel (T_{1GM} ≈973 ms[26]) associated with a relative B_1^+ variation of +20% (i.e. 120%), has a signal intensity of 0.052; which without B_1^+ correction would result in an underestimated T_{1GM} of about 948 ms (~ -3%). Same illustration goes for a voxel of SC WM (T_{1WM} ≈876 ms[26]) associated with a B_1^+ variation of -30% for instance (i.e. 70%), leading to an overestimated T_{1WM} of about 910 ms (~ +3%). Given these relatively small errors on T_1 estimation for the range of B_1^+ variation observed *in vivo*, one could consequently choose to apply the B_1^+ correction for potential residual effect or not.

Curves illustrating the brain protocol proposed by Marques et al.[16] at 3T together with the same brain protocol but modified to cope with our SC needs are also shown to illustrate the need for optimization when dealing with different anatomical regions (Fig. 2a). While such a protocol led to a flatter signal curve and therefore would allow improved WM/GM signal

difference (maximal contrast of 0.09), it would have led to larger uncertainties for T_1 value measurements above 1200 ms (due to non-bijective behavior), which potentially correspond to pathological T_1 values or pixels contaminated by PVE with CSF.

Fig. 3 illustrates the efficacy of the custom B_1^+ correction on the 6 MP2RAGE datasets acquired with various voltages from 70% to 120% of the nominal reference value (100% ⇔ 45°, nominal flip angle value, targeted at C_3 level). The curves from the graph to the left represent the uncorrected $T_1^{MP2RAGE}$ values whilst those from the right represent the B_1^+-corrected values. For the sake of clarity, data from tubes #7, #9, #12, #13 and #17 are not shown here. Within the 70%-120% range of B_1^+ variation investigated, $T_1^{MP2RAGE}$ values from all twelve tubes presented an average variation of +0.57% ([-4.5% to 5.6%], RMSE=32.84 ms) and -0.01% ([-1.3% to 1.0%], RMSE=5.30 ms) as compared to the nominal $T_1^{MP2RAGE}$ (100% of reference voltage) before and after B_1^+ correction respectively. In addition, the [min-max] range of mean $T_1^{MP2RAGE}$ value per tube across all 6 acquisitions (horizontal shaded bars on *Fig. 3c* and *d*) were found greatly reduced after the B_1^+ correction. All these results support the efficacy of the B_1^+ correction method.

To demonstrate the conformity of MP2RAGE-based T_1 values to gold standard T_1^{IRSE}, *Fig. 4a* shows a pixel-by-pixel plot of $T_1^{MP2RAGE}$ and T_1^{IRSE}. The $T_1^{MP2RAGE}$=T_1^{IRSE} line is shown in dashed black. Linear regression (red line) showed the high degree of agreement between the two techniques (slope: 1.0014, R^2:0.997) confirmed by the Bland-Altman representation in *Fig. 4b* showing a negligible bias (mean bias: 0.55) between the two measurements.

Finally, both *in vitro* T_1^{IRSE} and $T_1^{MP2RAGE}$ measurements were found highly reproducible. COV and in-ROI standard deviations were estimated to 2.94% (range: [2.21% - 3.75%]) and 0.66% (range [0.42% - 1.35%]), respectively for the $T_1^{MP2RAGE}$ and 2.15% (range: [1.66% - 3.07%]) and 0.96% (range: [0.49% - 1.46%]), respectively for T_1^{IRSE}.

3.2. ***In vivo* T_1 measurements**

Fig. 5 shows a representative dataset of the T_1-weighted $MP2RAGE_{UNI}$ volume reconstructed online and the corresponding $T_1^{MP2RAGE}$ map (without B_1^+ correction) in all three orientations (sagittal, coronal and axial) allowing clear visualization of vertebral bodies, intervertebral disks and spinal cord. The butterfly-shaped GM, whose mask (derived from the probabilistic atlas) is highlighted with the dotted line boundary in blue, can be distinguished in both axial images as compared to the surrounding WM. The brain was also covered in the

acquisition but not exploited in the present study. *Fig. 6* illustrates a typical *in vivo* B_1^+ map showing the variation pattern in the cervical SC when targeting flip angle (100% B_1^+) around C_3. Boxplots of the B_1^+ variation in all ten subjects show reduced B_1 efficiency at lower cervical levels (69% at C_7) and slight increase at C_1-C_2 level (119% at C_1). Without B_1-correction, $T_1^{MP2RAGE}$ values from the whole WM at C_7 across the subjects would vary from (910ms ± 51ms) and (1055ms ± 139ms) with inter-individual mean $T_1^{MP2RAGE}$ values of (955ms ± 38ms) and mean in-ROI SD of 78ms (8.1% of the mean). After B_1-correction, they varied between (865ms ± 40ms) and (1011ms ± 134ms), with a mean of (915ms ± 37ms) and a mean in-ROI SD of 73ms (8.0% of the mean).

In vivo corrected $T_1^{MP2RAGE}$ measurements were found highly reproducible. All COV values were found to be lower than 5% in all ROIs at all cervical levels (range [0.97-4.65]), with highest COV values (> 2.5%) mostly found at lower cervical levels (C_5 to C_7). *Table 1* summarizes the global COV values, averaged across all cervical levels, for each ROI (aGM, LMT, PST and whole WM), along with the mean in-ROI standard deviation values (expressed as a ratio relative to mean $T_1^{MP2RAGE}$ value). In-ROI standard deviation values were found higher than COV values.

3.2.1. Level-, tract- and age-related variations of $T_1^{MP2RAGE}$ values

Average $T_1^{MP2RAGE}$ group maps in the template space for both young and elderly subjects per cervical level are presented in *Fig. 7*, along with examples of individual maps. The butterfly-shaped GM can be visualized at each cervical level, particularly in the young group dataset. The contrast between the LMT and PST tracts can also be clearly visualized. For detailed $T_1^{MP2RAGE}$ data per ROI and cervical level from the two age groups, the reader is referred to *Supplementary Table.*

Results of three-way ANOVA highlighted significant effects of age group, ROI and cervical levels on $T_1^{MP2RAGE}$ values. No significant second or third effects were found. When comparing the two age-groups, $T_1^{MP2RAGE}$ values decrease trends in elderly subjects as compared to young ones were found in every ROI at every cervical level especially at upper levels (C_1-C_3) in the order of -3%. However, no statistical significance was found. As for the cervical level influence, *Fig. 8* shows the pattern of $T_1^{MP2RAGE}$ variations along the cervical cord for each age-group and ROI. Although no significant differences were found between $T_1^{MP2RAGE}$ values from the different levels along the cord, a U-shaped trend can be observed

from upper to lower levels, particularly pronounced in the WM tracts. Finally, considering ROI effect on $T_1^{MP2RAGE}$ values, *Fig. 9* plots mean $T_1^{MP2RAGE}$ values (n=10 subjects) per ROI (aGM, LMT, PST) at each cervical level (C_1 to C_7). Results of Steel-Dwass all pairs tests showed significant differences between aGM and LMT for all cervical levels ($0.006 \leq p \leq 0.037$), but only differences at upper levels remained significant after Bonferroni correction. $T_1^{MP2RAGE}$ values from LMT were also found lower than that of PST at C_2 ($p=0.037$), C_3 ($p=0.013$) and C_4 ($p=0.019$) but the differences were not significant after Bonferroni correction.

3.2.2. Morphological measurements

CSA values extracted from automated SC segmentation on $T_1^{MP2RAGE}$ map were found highly correlated to those extracted from the anatomical T_1-weighted GRE_{TI2} volume, confirmed by linear fit results (*Fig. 10a*, slope: 0.83, R^2=0.9, p<.0001). However, the Bland-Altman plot (*Fig. 10b*) shows evidence of a systematic bias (mean bias: -7.03, regression line y=-0.14*x +1.81, R^2=0.17, p=0.0005) between the two measurements, i.e., CSA values from the $T_1^{MP2RAGE}$ map were systematically lower than that from GRE_{TI2} map by 7 mm^2 in average. When used to preliminarily investigate age-related morphological changes at each cervical level, GRE_{TI2}-based CSA values were found decreased in elderly subjects compared to young ones (*Fig. 10c*). Nonetheless, no significant decrease was found from the Wilcoxon's rank tests.

4. Discussion

The purpose of this study was to use the recently proposed MP2RAGE sequence to obtain reliable volumetric T_1-mapping of the whole cervical cord at 3T within a clinically acceptable scan time at a sub-millimetric resolution. A validation experiment was performed on a dedicated phantom by comparing T_1-values obtained from the MP2RAGE sequence to the gold-standard IR-SE protocol. The optimized MP2RAGE protocol was then applied *in vivo* and combined with an automated processing pipeline based on dedicated SC MR templates and atlases to probe regional microstructural organization of the healthy aging SC, while avoiding bias associated to manual ROI delineation.

4.1. MP2RAGE parameters in this study

The range of T_1 values for which we wanted to ensure a bijective behavior and precise $T_1^{MP2RAGE}$ determination was motivated by the future use of the MP2RAGE sequence in a clinical context. For instance, a previous study investigating multiple sclerosis reported values of T_1 ranging from 500 to 1700 ms in the brain at 3T[5]. Our choice was also motivated by the need for unambiguous T_1 determination within the CSF to avoid PVE contamination in pixels at the interface of WM and CSF and in pathologies in which CSF leaks within the cord or edema is present, such as in syringomyelia or *neuromyelitis optica* spectrum disorders. As an example, the application of the brain protocol described in[16] would have led to a non-bijective behavior of the $MP2RAGE_{UNI}$-$T_1^{MP2RAGE}$ relationship, and therefore to a more ambiguous estimation for T_1 values close to and above 1600 ms (see purple and magenta curves on *Fig. 2*). Another criteria that we chose to apply to our study was to limit the B_1^+ variation effect on $T_1^{MP2RAGE}$ measurements, motivated by the need for precise T_1 quantification along the cervical cord allowing for characterization of microstructural changes encountered in diffuse pathology. Overall, these choices and the resolution vs acquisition time compromise led to a small possible range for the MP2RAGE parameters.

In the current study, under the maximum GM-WM signal difference criteria, the parameters optimization led to protocol #1 (α_1/α_2=8°/5° and TI_1/TI_2= 650 ms/2000 ms), but this protocol potentially leads to subsequent ambiguous T_1 estimation in CSF and pathological tissues due to non-bijective behavior with reduced B_1 efficiency up to 70%, a value that could be observed *in vivo* at lower cervical levels (C_6-C_7). Furthermore, within the [70%-120%] range of B_1^+ variation, this protocol led to ±6% of simulated $T_1^{MP2RAGE}$ measurement errors in the SC GM and WM. Therefore, when including the low sensitivity to B_1^+ variation criteria, the optimum protocol was protocol #2, with a reduced α_1 of 4° as compared to protocol #1 (the $MP2RAGE_{UNI}$ signal indeed shows a higher sensitivity to B_1^+ when the α_1 value is increased). For protocol #2, the GM-WM signal difference was 0.06, and more importantly, the simulated $T_1^{MP2RAGE}$ measurement error was about ±3% for the range of B_1^+ variation observed *in vivo* ([70%-120%]), making this protocol more suitable for *in vivo* application.

When applied for validation to a phantom, this protocol provided $T_1^{MP2RAGE}$ values that were found in a close to perfect pixel-wise agreement with the gold standard inversion-recovery T_1^{IRSE} values (see *Fig. 4*, $R^2=0.997$) with a mean measurement bias of 0.55±20.29ms. Furthermore, the phantom results were found highly reproducible, with an average COV of 2.94% and in-ROI standard deviations of 0.66% of mean values.

4.2. B_1^+ inhomogeneity and MP2RAGE imaging

At high fields (≥ 3 T), the shorter radiofrequency wavelength leads to transmit field inhomogeneities, i.e. flip angle/B_1^+ variations across the imaged object, that could be prejudicial to image signal homogeneity or quantitative parameters derived from biased images[39]. These inhomogeneities could be further accentuated in the SC by the proximity of large bony structures and the flowing cerebrospinal fluid. In our *in vivo* 3T study, the reference voltages were determined during automated scanner adjustments, and the range of observed B_1^+ relative variation throughout the cervical SC could reach up to [70% – 120%], found at C_7 and C_1/C_2, respectively.

With protocol #2, the $T_1^{MP2RAGE}$ measurement error within the observed range of B_1^+ variation was about ± 3% for SC tissues. With this range of measurement error, this protocol could be used without further B_1^+ correction. However, we would still recommend correcting for B_1^+ effects. Indeed, the custom LUT-based B_1^+ correction method proposed here exhibited very good efficacy when applied to *in vitro* data (B_1^+ related $T_1^{MP2RAGE}$ error measurements relative to nominal $T_1^{MP2RAGE}$ values before and after correction of +0.57% ([-5% to 6%], RMSE=32.84 ms) and -0.01% ([-1% to 1%], RMSE=5.30 ms), respectively), motivating its use for *in vivo* data.

Another method to correct for B_1^+ bias could be to introduce a third readout at a third inversion time from which a B_1^+ and a T_1 map would be calculated[40–42]. This would require additional and more complex sequence parameters optimization. Given the results obtained in the present study, the LUT approach using an additional B_1^+-map acquisition appears as a good alternative to enable bias-free MP2RAGE acquisitions, adding only one minute of acquisition time. Note that a 2D magnetization-prepared turbo-FLASH B_1^+-mapping[33] method was used in this study but other B_1^+-mapping methods, such as the recently proposed SA2RAGE (Saturation-prepared with 2 rapid Gradient Echoes)[43] or the AFI[44] (Actual Flip-angle Imaging) could also be of great interest and should be considered in future studies. It is also worth mentioning that, alternatively, an increased $MP2RAGE_{TR}$ could also be used, resulting in a reduction of the $MP2RAGE_{UNI}$ signal sensitivity to B_1^+ inhomogeneity (e.g. less than ±1.9% T_1 measurements errors within the [70%-120%] range of B_1^+ variation for TR=5s), at the expense of a slight increase in the acquisition time (9:10 min for TR=5s vs. 8:18 min in our study with T_1 and B_1 measurements).

4.3. Accuracy and reproducibility of *in vivo* $T_1^{MP2RAGE}$ measurements

Being able to measure T_1 values *in vivo* with the highest reproducibility and accuracy available is very important since these values should closely reflect the underlying tissue microstructure and their magnetic properties. IR-SE sequences are the gold standard methods to perform tissue T_1 mapping but scan times for such acquisitions are prohibiting for potential clinical applications (for example, in this study, acquisition time for the IR-SE on the phantom was 20 min per TI for a single slice acquisition). Another emerging alternative approach could be MR fingerprinting, but SC implementation has not yet been proposed although applications to the brain are currently already available with in-plane spatial resolution in the order of 1x1 mm^2 [6,45].

With a sub-millimetric spatial resolution suitable for SC investigation, a less than 10 min acquisition, and a relatively smooth post-processing pipeline, the MP2RAGE sequence allowed highly reproducible *in vivo* T_1 quantification in the cervical SC with mean and max COV of 2% and 5% respectively, within the different ROIs (cf. *Table 1*). Moreover, the MP2RAGE sequence parameters were optimized to allow unambiguous T_1 values determination from 500 ms to 3000 ms (see *Fig. 2*), hence covering the full extent of T_1 values reported for human brain and SC at 3T, even in pathological contexts. The *in vivo* in-ROI standard deviations were found in average in the order of 7% of mean T_1 values (see *Table 1*), for all regions of interest.

Table 2 summarizes T_1 values reported in this study and other studies of the literature performed in the cervical SC at 3T using various techniques. The T_1 values obtained in this study exhibited a similar pattern of T_1 values distribution across the different regions of the cervical SC as the values reported by Smith et al.[26], i.e. $T_{1LMT} < T_{1WM} < T_{1PST} < T_{1GM}$ using both IR-EPI and GRE-based techniques. However, T_1 values measured in SC WM are longer in the current study. This difference could arise from the fact that in[26], SC WM values were obtained by averaging dorsal and lateral columns T_1 values, whereas our values were extracted from the whole WM ROI, hence also including the anterior WM regions which were reported by Lévy et al.[25] to have longer T_1 values of 1006.8±168ms (*vs.* 971.6±64.5ms in lateral tracts). Furthermore, T_1 values in GM were found shorter in the present study. This may arise from the difference between manual and template-based ROI delineation. This more probably comes from the fact that in their study, whole GM was considered whereas in the present study, only anterior GM was studied due to posterior GM potentially suffering from GM/WM PVE. T_1 values reported in[24,25,27] were found higher than[26] and our study in all

ROIs. However, in the study of Battiston et al., the similarity of GM/WM values as well as larger standard deviations, which may come from the thicker slices, could induce some CSF/WM and WM/GM partial volume effect in the rostro-caudal direction if not strictly parallel to the cord axis, hence biasing values in the different compartments. For the studies from Lévy et al. and Duval et al., the difference could likely be explained by the use of VFA-based techniques, which usually overestimate T_1 values when not corrected for B_1^+ variations[9]. As for the study of Samson et al., their reported T_1 values using a multi-echo FLASH are much higher than those reported in all other studies.

4.4. MP2RAGE-based SC microstructural characterization

Microstructural alterations of the aging brain have been previously largely investigated using quantitative MRI[6,29,30,46]. Characterization of the aging SC, on the other hand, generally lag behind the brain and the few studies conducted so far have mostly focused on morphological measurements reporting age-related atrophies of GM and whole SC[37,47–49]. In the current study, MP2RAGE acquisitions allowed to evaluate SC morphology using the automated SC segmentation on T_1-weighted GRE_{TI2} image, whose contrast is similar to the MPRAGE, commonly used in clinical studies and previously validated with regards to manual delineation[50]. The resulting CSA values exhibited decrease trends, without statistical significance, in elderly subjects when compared to young ones, at all cervical levels from C_1 to C_7, suggesting SC atrophy, in line with previous reports. It is worth noting that CSA extracted from SC segmentation based on quantitative $T_1^{MP2RAGE}$ were highly correlated to those from GRE_{TI2}, but with a mean bias of -7 mm^2 relative to the CSA GRE_{TI2}, suggesting that conventional tool and default options for cord segmentation (PropSeg[35]) have to be slightly optimized for this new contrast. This optimization was beyond the scope of this study, as CSA could be extracted from the GRE_{TI2} volume.

Several studies have also used quantitative SC MRI, mostly diffusion tensor imaging[48,51,52] and magnetization transfer-based techniques[25,48] to study microstructural changes occurring with age, with evidences supporting hypotheses of demyelination and destructuration. To the best of the authors knowledge, the study from[25] is the first study to evaluate SC T_1 relaxometry variation with age. This latter study did not find evidence of significant T_1 variations whereas brain studies reported age-related T_1 decrease in the GM[53] and T_1 increase in the WM[54]. In this preliminary work, slight trends of T_1 value decrease were found in both anterior GM and WM tracts in the elderly group, however given the small number of

participants in our study, this should be further explored. Higher inter-subject variability of T_1 data were particularly noticed on both graphs and mean T_1 maps with less sharp GM/WM boundaries than in younger subjects, which could express different degrees of ageing impairments (linked to sport or professional activities for example).

Finally, our preliminary tract-based analysis also exhibited trends of lower T_1 values in LMT (motor) tracts as compared to that in PST (sensory) tracts. This is in agreement with previous studies reporting higher myelination in lateral motor tracts as compared to posterior sensory tracts[24,25,48], which would lead to lower T_1 values, according to[55]. As for the vertebral level influence on T_1 values, a U-shaped pattern in the rostro-caudal direction could be observed, although no statistical differences were found as it was the case in previous reports[23,27]. As mentioned above, these should also be reinvestigated while considering a larger cohort.

5. Conclusion

In this work, MP2RAGE-based T_1-mapping was optimized for sub-millimetric SC imaging for the first time at 3T. Using an additional B_1^+ correction method, 3D T_1-weighted anatomical imaging and unbiased T_1-mapping of the entire cervical cord were obtained within a scan time compatible with clinical research. Combined with an atlas-based approach, highly reproducible and accurate T_1 measurements within specific regions of the cervical white matter and anterior gray matter horns were obtained, highlighting preliminary regional and age-related differences.

Benefiting from a very high reproducibility, the MP2RAGE protocol proposed here could be of particular interest in the characterization of early and longitudinal SC microstructural changes in different diseases involving the spinal cord such as Multiple Sclerosis and Amyotrophic Lateral Sclerosis. Alone or associated with other quantitative and more specific MR imaging such as diffusion tensor imaging, myelin imaging using either conventional/inhomogeneous magnetization transfer or myelin water imaging in a multi-parametric approach, this technique could help investigating the different underlying pathophysiological mechanisms.

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Conflict of interest:

Tobias Kober is an employee of Siemens Healthcare AG Switzerland, who provided sequence support with the MR technique but was not involved in data acquisition and analysis. No conflicts of interest are declared for the remaining authors.

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ROI	aGM	LMT	PST	Whole WM
COV (%)	2.46 ± 0.67 [1.44 - 3.26]	3.08 ± 1.04 [0.97- 4.65]	2.34 ± 0.79 [1.21 - 3.98]	1.88 ± 0.30 [1.46 - 2.25]
In-ROI SD (%)	3.92 ± 1.21 [1.84 – 8.93]	9.74 ± 3.15 [4.65 – 18.44]	6.89 ± 3.88 [2.86 – 20.11]	7.92 ± 1.24 [4.76 – 10.91]

Table 1: *In vivo $T_1^{MP2RAGE}$ reproducibility. Mean coefficient of variation (COV, in %) of $T_1^{MP2RAGE}$ values are presented together with mean in-ROI standard deviations (SD, computed as the ratio of $T_1^{MP2RAGE}$ SD and mean values) from the different regions of interest (anterior gray matter (aGM), lateral motor tracts (LMT), posterior sensory tracts (PST) and whole white matter (WM), all cervical levels considered, from n=3 subjects examined at 3 different time-points.*

References	Sequence type / Levels	Population age (years) (number)	Image resolution (mm^3)	T_1 GM (ms)	T_1 WM (ms)	T_1 Dorsal column (ms)	T_1 Lateral column (ms)
Smith et al. (2008)	IR-EPI C_3	31±6 (n=6)	1x1x5	972±36	876±27	900±17	863±23
Smith et al. (2008)	GRE VFA C_3	31±6 (n=6)	1x1x4	994±54	838±54	853±68	830±47
Samson et al. (2013)	Multiecho-FLASH C_1-C_5	36±12 (n=13)	1.28x1.28x3	1815±170	-	1735±205	1650±220
Battiston et al. (2017)	IR-ZOOM-EPI C_1-C_7	[27-37] (n=5)	1x1x5	1136±91	-	1150±103	1109±80
Duval et al. (2017)	VFA-FLASH C_2-C_5	29±14 (n=9)	0.8x0.8x5	-	1290±130	-	-
Lévy et al. (2018)	VFA-FLASH C_2-C_4	57 [21-72] (n=16)	0.9x0.9x5	-	1011±61	1068±64	-
This study	MP2RAGE C_3	29±4 (n=5)	0.9x0.9x1	927±23	911±29	914±26	874±36
This study	MP2RAGE C_1-C_7	29±4 (n=5)	0.9x0.9x1	943±32	919±24	925±29	888±29

Table 2: *Comparison of T_1 values measured in this study and those found in the literature for cervical spinal cord at 3T. Values are reported in ms (mean ± standard deviation). Population age are reported as mean± standard deviation or [min-max] range.* ***IR:*** *Inversion Recovery;* ***EPI:*** *Echo Planar Imaging;* ***GRE****: Gradient Echo;* ***FLASH:*** *Fast low-angle shot;* ***ZOOM:*** *Zonally oblique-magnified multi-slice;* ***VFA:*** *Variable Flip Angle;* ***MP2RAGE****: Magnetization Prepared 2 Rapid Acquisition Gradient Echoes;* ***GM:*** *gray matter;* ***WM:*** *white matter.*

Figures

Figure 1: Contour plots showing the simulated SC GM-WM contrast *(signal intensity difference between SC GM and WM) as a function of flip angles α_1 and α_2 (**left**) and inversion times TI_1 and TI_2 (**right**). Two protocols with different parameter subsets are identified in both graphs: Protocol #1 (α_1/α_2=8°/5° and TI_1/TI_2=650ms/2000ms) rendering the maximal signal difference (0.08) but with higher B_1^+dependency (see Fig. 2b); and Protocol #2 (α_1/α_2=4°/5° and TI_1/TI_2=650ms/2000ms) rendering a signal difference of 0.06 but much less sensitive to B_1^+ variation (see Fig. 2c).*

Figure 2: $T_1^{MP2RAGE}$/MP2RAGE$_{UNI}$ signal intensity relationship and effect of B_1^+ inhomogeneity on $T_1^{MP2RAGE}$ estimation. (a): *Plots of $T_1^{MP2RAGE}$ values as function of MP2RAGE$_{UNI}$ image intensity estimated using Bloch equations. The red dotted lines correspond to the expected SC GM and WM T_1 values reported in [26]. **Green curve (Protocol #1):** Protocol with optimal sequence parameters providing the maximum GM/WM contrast. **Blue curve (Protocol #2):** protocol used in this study; **the purple curve** shows what would be obtained using optimal parameters proposed by Marques et al. for the brain in [16](MP2RAGE$_{TR}$=5s; GRE$_{TR}$=7ms; GRE$_n$=160 excitations per GRE module; TI_1/TI_2=700ms/1500ms; α_1/α_2=4°/5°, spatial resolution = 1x1x1mm^3) without further optimization. The **pink curve** indicates what would be obtained with this latter protocol but modifying MP2RAGE$_{TR}$, GRE$_{TR}$ and GRE$_n$ to suit our SC needs, i.e. sub-millimetric spatial resolution and T_{acq} less than 10 minutes. **(b):** Effect of B_1^+-variation (70% to 120%) on Protocol #1; **(c):** Effect of B_1^+-variation (70% to 120%) on Protocol #2 (used in this study); **(d):** Zoom on the black box of Fig. (c) so as to better illustrate the B_1^+ effect on T_1 estimation in GM and WM using protocol #2.*

Figure 3: Phantom experiments to validate the custom B_1^+ correction method. Top*: from left to right: Eurospin T_1 phantom containing twelve tubes filled with gadolinium-doped agar gel; theoretical T_1 mean and standard deviation specifications (in ms) for each tube, provided by the manufacturer (Temperature: 23°C, last phantom QA control in 2011); and the B_1^+-corrected $T_1^{MP2RAGE}$ map. It is worth noting that IR-SE and MP2RAGE T_1 values were not compared to the values provided by the constructor due to experimental temperature differences and potential time alteration of the phantom. **Bottom left:** Curves corresponding to mean uncorrected $T_1^{MP2RAGE}$ values for 7 phantom tubes with the prescribed B_1^+ variation (Tubes #7, #9, #12, #13 and #17 are not shown for easier visualization). The range of B_1^+ variation considered here were chosen so as to cover the range of variation observed in vivo ([69% - 119%], see Fig. 6). **Bottom Right:** Curves corresponding to B_1^+-corrected $T_1^{MP2RAGE}$ values. Horizontal shaded bars correspond to [min-max] range of observed $T_1^{MP2RAGE}$ values for each tube across the relative B_1^+ variation range. The dashed vertical line corresponds to the $T_1^{MP2RAGE}$ values obtained with 100% of nominal B_1^+.*

Figure 4: $T_1^{MP2RAGE}$ measurement validation on phantom. (a): *Pixel-by-pixel plot of B_1^+-corrected $T_1^{MP2RAGE}$ and T_1^{IRSE} values from all tubes, over three different timepoints. The dashed black line corresponds to $T_1^{MP2RAGE}$=T_1^{IRSE}. Linear regression fit between $T_1^{MP2RAGE}$ and T_1^{IRSE} is illustrated by the red trend line and associated coefficient of correlation R^2. **(b):** Bland-Altman plot of absolute differences between $T_1^{MP2RAGE}$ and T_1^{IRSE}. Mean bias and 95% limits of agreement are shown with horizontal green lines.*

Figure 5*: **Representative in vivo dataset including**, **from left to right,** sagittal, coronal and zoomed axial view at C_2 of (**from top to bottom**) the acquired GRE$_{TI1}$ and GRE$_{TI2}$ volumes, the resulting T_1-weighted MP2RAGE$_{UNI}$ volume reconstructed online and the corresponding $T_1^{MP2RAGE}$ map without B_1^+ correction. A manually-drawn GM region boundary (in blue) has been added to the MP2RAGE$_{UNI}$ image for better visualization.*

Figure 6: In vivo B_1^+ variation in the cervical spinal cord. ***Left:*** *illustration of an acquired B_1 map superimposed on an anatomical T_2-weighted sagittal image for visualization, showing the B_1^+ variation pattern throughout the spinal cord and particularly the reduced B_1 efficiency observed at lower cervical levels (C_6-C_7).* ***Right:*** *Relative B_1^+ variation (expressed in % relative to the nominal B_1^+ flip angle (100%)) at each cervical level from all ten subjects. The box plots represent the minima, first quartile (25%), the median, the third quartile (75%) and the maxima from bottom to top, respectively. Average values per cervical level are also reported.*

Figure 7: Age-, tract- and cervical level-related T_1 variation in the cervical spinal cord. ***From left to right****: Anatomical T_2*-weighted AMU_{40} template image; average T_1 map for the young group; average T_1 map for the elderly group; representative individual T_1 map of a young subject (Male; 22 years old); representative individual T_1 map of an elderly subject (Female; 57 years old). Rows correspond to the vertebral levels from C_1 to C_7.*

Figure 8: Evolution of $T_1^{MP2RAGE}$ values (in ms) versus cervical level for every region of interest *(anterior gray matter (aGM), lateral motor tracts (LMT) and posterior sensory tracts (PST)) for young (left, n=5, <35 years old) and elderly (right, n=5, >50 years old). The box plots represent the minima, first quartile (25%), the median, the third quartile (75%) and the maxima from bottom to top respectively.*

Figure 9: Regional variation of $T_1^{MP2RAGE}$ values *(anterior gray matter (aGM), lateral motor tracts (LMT) and posterior sensory tracts (PST)) at each cervical level, all subjects considered (n=10). The boxplots represent the minima, first quartile (25%), the median, the third quartile (75%) and the maxima from bottom to top respectively. P-values are reported when the results of Steel-Dwass all pairs tests are statistically significant. P-values in light gray color indicate significant differences between aGM and LMT, p-values in black, between LMT and PST.* ***†*** *indicates statistical differences that survive Bonferroni correction for multiple comparisons (adjusted Bonferroni p<0.0071)*

Figure 10: MP2RAGE-based morphological measurements. (a): *Linear regression between $T_1^{MP2RAGE}$- and GRE_{TI2}-based cross-sectional areas (CSA, in mm^2) showing the high degree of correlation between the two measurements.* ***(b):*** *Bland-Altman plot showing absolute differences between the two measurements. Mean bias and 95% limits of agreement are also reported with blue lines.* ***(c):*** *GRE_{TI2}-based SC CSA values in the two age-groups as a function of cervical level, from C_1 to C_7. Boxplots represent the minima, first quartile (25%), the median, the third quartile (75%) and the maxima from bottom to top respectively.*