

An optimized MP2RAGE sequence for studying both brain and cervical spinal cord in a single acquisition at 3T

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1 2	An optimized MP2RAGE sequence for studying both brain and cervical spinal cord in a single acquisition at 3T.
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44 Abbreviations

- 45 MP2RAGE: Magnetization Prepared 2 Rapid Acquisition Gradient Echo
- 46 TI1/TI2: First and second inversion times
- 47 α_1/α_2 : First and second RAGE flip angles
- 48 cSC: Cervical Spinal Cord
- 49 MS: Multiple Sclerosis
- 50 ALS: Amyotrophic Lateral Sclerosis
- 51 CNR: Contrast to Noise Ratio
- 52 WM: White Matter
- 53 GM: Gray Matter
- 54 CSF: Cerebrospinal Fluid
- 55 ROI: Region of Interest
- 56 SD: Standard Deviation
- 57 COV: Coefficient of Variation
- 58 CST: Corticospinal Tracts
- 59 PST: Posterior Sensory Tracts
- 60 LST: Lateral Sensory Tracts
- 61 RST: Reticulo/Rubrospinal Tracts
- 62 Pr: Protocol
- 63 FOV: Field of view
- 64 EPI: Echo Planar Imaging
- 65 FLASH: Fast Low- Angle Shot
- 66 TR: Repetition Time
- 67 PAT: Parallel Acquisition Technique
- 68 69

70 Abstract

- 71
- Magnetization Prepared 2 Rapid Acquisition Gradient Echo (MP2RAGE) is a T_1 mapping technique that has been used broadly on brain and recently on cervical spinal cord (cSC).
- 74 The growing interest for combined investigation of brain and SC in numerous pathologies of
- 75 the central nervous system such as multiple sclerosis (MS), amyotrophic lateral sclerosis
- 76 (ALS) and traumatic injuries, now brings about the need for optimization with regards to this
- specific investigation. This implies large spatial coverage with high spatial resolution and
- short acquisition time, high CNR and low B_1^+ sensitivity, as well as high reproducibility and robust post-processing tools for T_1 quantification in different regions of brain and SC.
- In this work, a dedicated protocol (referred to as Pr-BSC) has been optimized for simultaneous brain and cSC T_1 MP2RAGE acquisition at 3T. After computer simulation optimization, the protocol was applied for in vivo validation experiments and compared to previously published state of the art protocols focusing on either the brain (Pr-B) or the cSC (Pr-SC). Reproducibility and in-ROI standard deviations were assessed on healthy volunteers in the perspective of future clinical use.
- The mean T_1 values, obtained by the Pr-BSC, in brain white, gray and deep gray matters were: (mean ± in-ROI SD) 792±27 ms, 1339±139 ms and 1136±88 ms, respectively. In cSC, T_1 values for white matter corticospinal, posterior sensory, lateral sensory and rubro/reticulospinal tracts were 902±41 ms, 920±35 ms, 903±46 ms, 891±41 ms, respectively, and 954±32 ms for anterior and intermediate gray matter. The Pr-BSC protocol showed excellent agreement with previously proposed Pr-B on brain and Pr-SC on cSC, with very high inter-scan reproducibility (coefficients of variation of 0.52±0.36% and 1.12±0.62%
- 93 on brain and cSC, respectively).
- This optimized protocol covering both brain and cSC with a sub-millimetric isotropic spatial resolution in one acquisition of less than 8 minutes, opens up great perspectives for clinical applications focusing on degenerative tissue such as encountered in MS and ALS
- 96 applications focusing on degenerative tissue such as encountered in MS and ALS.
- 97

98 Keywords

- 99 T₁ mapping, Magnetization Prepared 2 Rapid Acquisition Gradient Echo, Central Nervous
- 100 System, Brain, Cervical Spinal Cord
- 101

102 **1** Introduction

103

104 The T_1 relaxation time, also known as spin-lattice relaxation time, is a MR property of the 105 tissue that holds great potential in characterizing alterations such as demyelination, iron 106 deposition or structural changes occurring in pathologies like Multiple Sclerosis (MS) and 107 Parkinson's disease. Consequently, quantitative measurements of T_1 have been used widely 108 to study such pathologies [1]–[5].

109 There have been several techniques developed for measuring T_1 . To date, Spin-Echo Inversion Recovery (SE-IR) remains the gold standard; but it is not very practical for clinical 110 111 use because of its long acquisition time [6]. The variant of Inversion Recovery with EPI (IR-112 EPI) [7] and Look Locker technique with EPI readout [8] are much faster, but they could suffer from geometrical distortions caused by the static magnetic field inhomogeneities, 113 114 especially when covering a large field of view [9]. Other techniques proposed to date include 115 the variable flip angle (VFA) [10] techniques which are relatively fast and can acquire 3D T_1 116 maps in clinically feasible times, but the conventional VFA T₁ quantitative mapping could be

biased by imperfect spoiling of the transverse magnetization [11].

118 Meanwhile, the Magnetization Prepared 2 Rapid Acquisition Gradient Echo (MP2RAGE),

119 which is an IR-based technique that acquires two RAGE volumes from which a uniform 120 (UNI) image is derived and used to estimate the T_1 of the tissue, has been proposed [12]. The

technique has already been largely used in brain at 3T [13], [14] and 7T [15], [16] to study

122 pathologies like MS and it has shown to be effective in investigating the progression of

123 disease as compared to gold-standard sequences like DIR (Double Inversion Recovery) [17],

124 [18] and FLAIR (Fluid Attenuated Inversion Recovery) [19]. MP2RAGE was also used to 125 study the whole cervical spinal cord (cSC), first at 7T [20] and more recently at 3T [21], [22].

126 Concurrently, there has been a growing interest in studying the whole central nervous system 127 (CNS) in recent years. Indeed, investigating both brain and SC holds great potential in further 128 understanding pathophysiological relationships occurring in degenerative or traumatic 129 pathologies [23]–[27]. However, the large FOV required to capture the whole brain and cSC 130 and the high sub-millimetric resolution needed to investigate small structures of SC, 131 combined with B_0 inhomogeneities and various artifacts and potential distortions, turn 132 simultaneous brain and cSC imaging into a challenge.

The MP2RAGE technique was previously optimized for brain investigation at 3T [13] and 7T [28] based on CNR and limitation of B_1^+ sensitivity, hence providing "standard protocols" for brain applications. More recently, Rasoanandrianina et al. considered the T₁ values observed on cervical SC GM and WM and proposed a protocol for imaging cervical SC specifically[21]. Since the tissue constraints are not the same for brain and cSC, these protocols are not necessarily optimal to be used in simultaneous brain and cSC imaging.

139 The present work consequently focuses on an MP2RAGE protocol dedicated to both brain 140 and cSC by considering and examining a wider range of T₁s observed in CNS. Optimization 141 was performed through computer simulation for a higher contrast-to-noise ratio (CNR) while 142 limiting B_1^+ sensitivity. An automatic post-processing pipeline was additionally proposed to 143 quantify T₁ maps obtained from subjects on different regions of white matter (WM) and gray 144 matter (GM) on cSC, and WM, GM and deep GM on brain. T1 values were compared with 145 those from previous brain or SC studies. Furthermore, the inter-session reproducibility of the 146 technique was assessed for prospective clinical application on progressive degenerative 147 diseases.

149 2 Materials & Methods

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151 2.1 Simulation

Simulations mainly focused on CNR and sensitivity to B_1^+ , considering a 3D isotropic 152 acquisition allowing to cover both brain and cSC (sagittal orientation preferred here) with a 153 154 sub-millimetric resolution (0.9 mm here). Simulation were performed by varying the main parameters that determine the unique relationship between the UNI image and the T_1 map 155 156 [12]. The MP2RAGE repetition time (MP2RAGE TR) was varied between 4000 and 6000 ms using a 250 ms step. The number of excitations per RAGE module was set to 176 (required 157 158 value to cover the brain width, using a 6/8 partial fourier) and the TR was kept fixed at 6 ms. 159 The first and second inversion times (TI1/TI2) were then varied in steps of 50 ms. First and 160 second RAGE flip angles (α_1/α_2) varied from 3° to 15°. The five main parameters which are MP2RAGE TR, TI1/TI2 and α_1/α_2 were varied and CNR and signal variation with B_1^+ 161 162 inhomogeneity were investigated at the same time.

For that purpose, a broad range of T_1 values (between 500 ms and 3000 ms) was consequently considered for the simulations in order to cover values observed in both cord and brain. The T_1 values set for SC WM and GM were 880 ms and 970 ms according to Smith et al. [29], and for the Cerebrospinal Fluid (CSF), an upper T_1 of 3000 ms was considered for the simulation based on previous data acquired. The range of T_1 values also covered T_1 s observed on the brain (810 ms for WM, 1350 ms for GM, 1250 ms for Nucleus caudate and 1130 ms for Putamen [12]).

170 The CNR per unit time between two tissues was calculated based on the formulas described171 in Marques et al. [12] as:

172
$$CNR_{tissue1VStissue2} = \frac{MP2RAGE_{tissue1} - MP2RAGE_{tissue2}}{\sqrt{\sigma_{tissue1}^2 + \sigma_{tissue2}^2}} \cdot \frac{1}{\sqrt{MP2RAGE_{TR}}} (1),$$

173 with

174
$$\sigma_{tissue} = a \sqrt{\frac{(GRE_{TI1}^2 - GRE_{TI2}^2)^2}{(GRE_{TI1}^2 + GRE_{TI2}^2)^3}} (2),$$

175 with $MP2RAGE_{tissue1}$ and $MP2RAGE_{tissue2}$ the UNI signal in tissue 1 and tissue 2 176 respectively, $\sigma_{tissue1}$ and $\sigma_{tissue2}$ the noise propagation in tissue 1 and tissue 2, respectively, 177 GRE_{TI1} and GRE_{TI2} the volumes acquired at first and second inversion times (in each tissue) 178 and "a" the magnitude of the noise. In the simulation, the noise was considered to be of the 179 same magnitude in each tissue and therefore, for different protocols relative to each other, the 180 term "a" was not considered anymore.

181 When optimizing the protocols, maximization of CNR was performed emphasizing on the 182 WM/GM and WM/CSF on cSC, for which segmentation may be more problematic than in 183 the brain, using a global CNR defined as:

184
$$CNR = CNR_{GMvsWM}.CNR_{WMvsCSF}$$
 (3)

Finally, a B_1^+ map obtained and averaged from 3 healthy volunteers (same volunteers used later on for in-vivo experiments) was used to determine representative B_1^+ variations encountered in brain and cSC. As seen on Figure 1, in regions with the highest field inhomogeneities such as brainstem and cerebral cortex on brain, and C1 and C7 on the cord, a B_1^+ variation of $\pm 20\%$ can be observed and this value was subsequently used in the 190 simulation part. A T_1 estimation error of less than 10% was set as a criterion for this value 191 and considered for cSC WM, GM and brain WM, GM, and deep GM.

192 Sets of parameters ((α_1/α_2 , TI₁, TI₂, MP2RAGE TR) leading to a non-bijective behavior in 193 lower and upper T₁ boundaries (500 ms and 3000 ms) were removed.

194 Figure 2 shows the simulated relationship between the UNI signal and the T₁ values in normal conditions and under $\pm 20\%$ B₁⁺ variations for 4 different protocols. The first one (fig. 195 2a), with TI1/TI2 = 800/3500 ms; $\alpha_1/\alpha_2 = 6/3$; and MP2RAGE TR = 4750 ms, which 196 was named Pr-max, provided the highest simulated CNR, at the expense of acquisition time 197 198 (9.2 minutes). The second protocol (fig. 2b), $TI1/TI2 = 650/3150 \text{ ms}; \alpha_1/\alpha_2 =$ 199 5/3; MP2RAGE TR = 4000 ms named Pr-BSC, provided a high simulated CNR (though 200 13% lower than in Pr-max), while allowing to cover brain and cSC in less than 8 minutes. 201 The third and fourth protocols (fig. 2c & fig. 2d) were previously optimized for studying 202 brain [13], [16], and SC [21], [22], independently. Figure 3 shows the derivative of the UNI signal in relation with different T_1s (in optimal B_1^+ condition) for each protocol. This figure 203 shows the ability and performance of each protocol in tissue discrimination. Given its CNR 204 205 and acquisition time, Pr-BSC was kept for subsequent in vivo studies

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209 2.2 In-vivo experiment

Protocols Pr-BSC, Pr-SC and Pr-B were tested on healthy volunteers. Sequence parameters for each protocol are provided in table 1. Data were acquired on a 3T Siemens Verio scanner with 12-channel head and 4-channel neck coils (Siemens Healthineers, Erlangen, Germany). Three healthy volunteers (27, 37, 45 years old, 1M/2F) were scanned in three separate sessions with each protocol, to assess the inter-session reproducibility of each sequence. The local ethics committee of our institution approved all experimental procedures of the study, and written informed consent was obtained from each volunteer.

217 A B_1^+ map acquired using a preconditioning RF pulse with turboFLASH readout[30] with a 218 resolution of 5 mm isotropic was additionally used to correct T_1 maps.

The complete post-processing pipeline used to extract metrics in different brain and cSC 219 ROIs is shown in Figure 4. The first step consisted of the B_1^+ correction of the individual 220 221 quantitative T₁ maps using a 3D look-up table (LUT) providing relationship between UNI and T_1 values in the presence of B_1^+ variation. Then on brain, after anterior-posterior 222 223 commissure (AC-PC) alignment of images [31], the UNI-denoised image (provided by the 224 segmentation scanner) was used for of GM and WM with SPM 12 225 (https://fil.ion.ucl.ac.uk/spm) "New segment" tool [32] and for segmentation of deep GM structures (including Nucleus caudate, Putamen and Thalamus) with FSL-FIRST 226 227 (https://fsl.fmrib.ox.ac.uk/) [33]. Data were then registered to MNI-152 atlas using SyN-228 ANTS [34] and divided into different lobes of frontal, parietal, temporal and occipital by 229 ICBM MNI-152 lobes atlas [35], [36]. On SC, segmentation of the cord was first performed 230 using the spinal cord toolbox (SCT [37]), then the T_1 map was registered to PAM50 template, which is an unbiased multimodal MRI template of the SC and brainstem [38]. For T_1 231 232 quantification, PAM50 masks including gray matter anterior and intermediate, white matter 233 corticospinal, posterior sensory, lateral sensory and rubro/reticulospinal tracts were warped 234 back into the subject space.

The mean and standard deviation (SD) of the corrected T_1 quantitative map was calculated in each brain and cSC ROI for each session and subject. The SD is reported for each ROI (in-ROI SD), between different sessions for each subject (inter-session SD) and between different subjects (inter-subject SD). Reproducibility for each protocol was assessed using the coefficient of variation (COV), defined as mean/inter-session SD. Statistical analyses were performed by JMP, Version 9 (SAS Institute Inc., Cary, NC).

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243 **3 Results**

Figure 5 shows a representation of the UNI-denoised image on one subject for Pr-BSC and Pr-B on brain and Pr-BSC and Pr-SC on SC. The sub-millimetric resolution of the technique allowed us to capture different structures of brain and cSC.

To transpose the results of simulation, the CNR per unit time for in-vivo data was calculated

from the previously defined formulae (1), using the average and the SD of the UNI signal in a tissue of MB2BACE and a respectively. For the calls of simplicity a clobal CNB

tissue as $MP2RAGE_{tissue}$ and σ_{tissue} , respectively. For the sake of simplicity, a global CNR for the whole GM/WM in brain for all protocols, and GM/WM and WM/CSF on cSC for Pr-

SC and Pr-BSC on each subject was calculated, and the results are summarized in table 2.

The optimized Pr-BSC provided higher CNR for each subject in both brain and cSC.

Figure 6 shows the T_1 comparison between Pr-BSC and Pr-SC on cSC (fig. 6a) and Pr-BSC and Pr-B on brain (fig. 6b). An excellent agreement was seen on brain with a Pearson correlation coefficient of 0.99 and a Bias±LOA (Limits of Agreement)=4.0±28.1 ms. On SC, this correlation was found equal to 0.88 with a Bias±LOA=25.1±38.8 ms. It should be noted that the bias on SC is lower than the mean in POLSD observed in aSC (around 20 ms)

that the bias on SC is lower than the mean in-ROI SD observed in cSC (around 39 ms).

258 The average T₁ values found with Pr-BSC on different regions of WM and GM on brain and cSC are summarized in table 3, together with values reported previously in the literature. The 259 mean T₁ values observed with our optimized Pr-BSC in brain WM, GM and deep GM were 260 792±27 ms, 1339±139 ms and 1136±88ms, respectively. In the cSC, the values for WM 261 262 corticospinal (CST), posterior sensory (PST), lateral sensory (LST) and rubrospinal & 263 reticulospinal (RST) tracts were 902±41 ms, 920±35 ms, 903±46 ms, 891±41 ms, respectively, and 954±32ms for anterior & intermediate GM. No statistically significant 264 differences were observed between different cervical levels. Inter-subject, in-ROI and inter-265 266 session SD values are also reported. In average, the values were found in the order of 2.65%, 267 6.24% and 0.67%.

Finally, the inter-session COV, calculated for each ROI, is detailed in Figure 7. All three protocols demonstrated a great reproducibility in average (see fig. 7a), with the COV being slightly better for Pr-BSC (not statistically significant). The highest COV (lowest reproducibility) was lower than 3% and observed at the C7 SC level (fig. 7e).

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273 **4 Discussion**

In this work, a simulation-based parameter optimization led to the identification of a high resolution T_1 mapping MP2RAGE protocol with high contrasted UNI images covering both brain and whole cSC in a single acquisition.

The optimized Pr-BSC showed excellent agreement with the T_1 values obtained with the standard brain protocol (Pr-B) in all ROIs [13], [16]. On cSC, a small bias (25 ms, representing 2.8% of the mean T1) was observed as compared to the reference protocol [21],
which represents less than the average cSC in-ROI SD and was therefore not further
investigated.

The optimized Pr-BSC also demonstrated high inter-session reproducibility (with the lowest COV observed on brain WM and highest on the C7 spinal level), hence opening promising perspectives for longitudinal follow-up studies.

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286 It should be mentioned that Pr-SC originally proposed for the cord by Rasoanandrianina et al. 287 [21] incidentally covered brain, however cerebral T_1 values were not investigated in their 288 initial study. Here, a bias in the order of 20 ms (which is lower than in-ROI SD) was 289 observed when comparing Pr-SC to Pr-B, which was not further analyzed as our purpose was 290 to benefit from increased CNR. However, this indicates that Pr-SC could also be used for 291 brain investigation although not optimal, if subject to further investigation of potential bias in 292 T₁ estimation. Reciprocally, Pr-B partially covers the cSC (down to C4 level), however 293 quantification was not considered since whole cervical cord was required here. Brainstem and 294 cerebellum are also fully quantifiable with the MR protocols used in this study, subject to 295 additional postprocessing optimization not considered here.

296

Pr-BSC also provides an increased CNR as compared to Pr-B, which was initially optimized for both CNR and B_1^+ immunity. Here, CNR gain optimization made for Pr-BSC comes at an expense of B_1^+ immunity and further necessitates a B_1^+ correction strategy (as previously proposed by Massire et al. [20]). The different coil set ups (12+4 channel head and neck here, as compared to optimal 32 channel in the original study [13], [16]) may also have slightly influenced the results..

303

304 Finally, this feasibility study was performed on a small number of volunteers in order to test 305 and validate the optimized Pr-BSC, to investigate the reproducibility for longitudinal follow-306 ups, and to assess the performance of the automatic post-processing pipeline. Future studies 307 should now focus on the sensitivity of the technique to detect disease progression, to assess 308 therapeutical efficacy, inter-site reproducibility in the perspective of multi-centric studies and 309 to provide representative normative values. The recently proposed compressed sensing (CS-310 MP2RAGE) [39] technique could be considered to further reduce the acquisition time and 311 make it even more suitable for clinical practice.

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314 **5** Conclusion

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This work proposes an optimized protocol dedicated to sub-millimetric simultaneous brain and cSC T_1 MP2RAGE mapping at 3T, compatible with clinical scan time.

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The protocol showed excellent agreement with previously proposed protocols for brain and cSC independently. It also demonstrated high inter-scan reproducibility, hence opening up great perspectives for longitudinal clinical applications, especially in the context of neurodegenerative (MS, ALS) diseases and SC injuries.

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Tables 453 454 455

Table 1 : Parameters used in each protocol for brain and spinal cord imaging.

	TI1/TI2	α_1/α_2	MP2RAGE TR / Total acq. time	FOV	Resolution	PAT factor
Pr-BSC (this study)	650/3150 ms	5/3	4000 ms/ 7.8 min	315x262 mm	0.9 mm iso	2
Pr-SC [21], [22]	600/2000 ms	4/5	4000 ms/ 7.8 min	315x262 mm	0.9 mm iso	2
Pr-B [13], [16]	700/2500 ms	4/5	5000 ms/ 8.4 min	256x240 mm	1 mm iso	3

457 Table 2: CNR per unit time (which takes into account the MP2RAGE TR) calculated on each 458 subject for GM/WM on brain and cSC. The CNR GM/WM on brain was also calculated for 459 Pr-SC since this protocol allowed covering the brain. On the other hand, Pr-B could not cover the entire cervical cord so CNR for SC GM/WM was not calculated in that case. The 460 optimized Pr-BSC provided the highest CNR on each subject and on average for brain and 461 *cSC*, *separately*. *Please note that the coil set-up used here* (12+4 *channels for brain and cSC*) 462 463 is different from the 32 channel head-coil used in previous papers[13], [16] and might not be 464 optimal for Pr-B with regards to CNR. However, since the CNR reported in [13] are reported 465 as normalized by CNR of FLAIR images, a direct comparison is not possible here. 466

	CNR for brain GM/WM			CNR for SC GM/WM		CNR for SC WM/CSF	
	Pr-BSC	Pr-B	Pr-SC	Pr-BSC	Pr-SC	Pr-BSC	Pr-SC
Sub 1	1.75	1.45	1.60	0.27	0.23	3.14	2.50
Sub 2	1.67	1.46	1.61	0.29	0.27	2.82	2.64
Sub 3	1.57	1.46	1.51	0.29	0.28	3.90	3.51
Mean	1.66±0.09	1.45±0.01	1.57±0.05	0.28±0.01	0.26±0.02	3.28±0.55	2.88±0.54

468Table 3: Average T_1 values (in ms) obtained with Pr-BSC in this study on brain and SC and469comparison with values reported in previous studies either on the brain or the cord. For this470study, the standard deviations (in ms) are reported for inter-subject, in-ROI and inter-session471(mean of the individual inter-session SD). The inter-session SD is the lowest SD in all regions472(in this study), which shows a great robustness for the technique. For the other studies cited473in the table, the SD represents the inter-subject variation. A good agreement with previously474reported T_1 MP2RAGE values (Marques 2010[12], Rasoanandrianina 2019[21]) was

475 observed. CST: Corticospinal Tracts, PST: Posterior Sensory Tracts, LST: Lateral Sensory

476 Tracts, RST: Reticulo/Rubrospinal Tracts.

Brain								
This study	(mean±[inter-subject	SD; ROI SD; inter-session SD])	Marques 2010 [12] (MP2RAGE)	Wright 2008 [40] (MPRAGE)	Okubo 2015 [14] (MP2RAGE)			
	Frontal	787±[15;23;2]		840±50				
XX/X/I	Parietal	794±[8;23;2]	810 20					
VV IVI	Occipital	790±[10;30;2]	810±30					
	Temporal	797±[8;34;2]						
	Frontal	1312±[57;139;10]		1610±100	-			
CM	Parietal	1322±[50;136;11]	1250+50					
GM	Occipital	1318±[31;139;9]	1330±30					
	Temporal	1407±[50;135;10]						
	Caudate	1206±[18;65;6]	1250±70	1390±50	1217±30			
Deep GM	Putamen	1151±[51;84;4]	1130±70	1330±70	1095±31			
	Thalamus	1053±[22;115;7]	1080±70	-	1077±30			
		S	SC					
This study	(mean±[inter-subject	SD; ROI SD; inter-session SD])	Rasoanandrianina 2019 [14] (MP2RAGE)	Smith 2008 [29] (IR)	Battiston 2017 [41] (IR ZOOM-EPI)			
	CST	902±[18;41;10]	877±35		-			
XX/N/I	PST	920±[28;35;10]	920±37	976±27	-			
VV IVI	LST	903±[34;46;9]	-	8/0±2/	1110±83			
	RST	891±[25;41;9]	-					
GM	Anterior & Intermediate	954±[35;32;10]	934±33	973±33	1136±90			

Figures 478 479



(a) Individual B_1^+ maps acquired with preconditioning RF pulse with 481 Figure 1: 482 TurboFLASH Readout [30] on 3 healthy subjects. (b) Mean and (c) standard deviation of B_1^+ maps over 3 healthy subjects, presented in the ICBM MNI-152 [35], [36] and PAM50 [38] 483 484 spaces. It can be observed in (b) that the highest B_1^+ field inhomogeneities can be observed in brainstem and cerebral cortex on brain, and C1 and C7 on the cord and in these regions, a 485 486 B_1^+ variation of $\pm 20\%$ can be observed. In (c) the inter-subject variation of B_1^+ is less than 487 5%; however, it should be noted that with different morphologies (larger neck or longer 488 spine) this variation could be increased.



490 Figure 2: (a-d) Relationships between UNI signal and estimated T_1 values in normal 491 condition (green curve) and with $\pm 20\% B_1^+$ variation (blue/red curves). (a) The protocol Pr-492 max, derived from the CNR simulation optimization process, provides the highest CNR but at 493 the expense of acquisition time (9.2 minutes). (b) The protocol Pr-BSC provides a high CNR, 494 while allowing to cover brain and cSC in 7.8 minutes. Despite optimization, it should be 495 noted that a $\pm 20\% B_1^+$ variation for a T_1 of 1350 (brain GM) for instance, leads to an 496 estimation error of 8.7% in T_1 determination (i.e. up to 120 ms), which imposes the necessity 497 for B_1^+ correction for accurate T_1 mapping. Such variations for lower T_1 s are less as can be 498 seen and for example, for T_1 s of less than 1000 ms, we can expect an estimation error of less 499 than 5%. Pr-SC and Pr-B correspond to previously optimized protocols for studying (c) SC 500 [21], [22], and (d) brain [13], [16], independently, with acquisition time of 7.8 minutes and 501 8.4 minutes, respectively.





504 *Figure 3:* (*left*) *Derivative of the UNI signal along* T_1 *values (slope of the graphs in figure 2)* ; this graph provides indications on the specificity of each protocol and their performance in 505 506 discriminating between different tissues. The table (right) summarizes the absolute of that signal derivative for different T_{1s} found in brain and cSC tissues. For $T_{1s} < 1040$ ms, Pr-BSC 507 508 shows the highest (absolute) values and for $T_1s > 1040$ ms the Pr-max shows the highest 509 values. For the whole range, Pr-BSC shows higher values than Pr-SC and Pr-B, i.e. higher 510 ability to discriminate between different tissues. It should be noted that this advantage comes at the expense of a lower B_1^+ immunity which necessitates the implementation of a B_1^+ 511 512 correction strategy to avoid T_1 estimation biases.





515 Figure 4: Post-processing steps for brain and cSC, with indication of the main regions of 516 interest.



518 Figure 5: (a) Representation of UNI-denoised image (no unit) for Pr-BSC (FOV 315x262) 519 mm^2) and Pr-B (FOV 256x240 mm^2) on brain in sagittal and (b) coronal views. (c) 520 Representation of UNI-denoised image for Pr-BSC and Pr-SC in the axial plane at the C5 521 level, and (d) with a zoomed view along the cervical SC (C1, C5 and C7). In (a) the red box 522 represents the volume of interest in previous brain studies [13], [16], the blue box represents the volume of interest in previous cSC studies [21], [22] and the purple box shows how Pr-523 524 BSC covers both brain and cSC in a single acquisition. Moreover, Pr-BSC provided a nice 525 delineation between different structures of brain (yellow arrows) and on cSC, the yellow 526 arrows demonstrate the signal difference between GM and WM.



Figure 6: (a) comparison between Pr-BSC and Pr-SC on different ROIs of cSC; (b) comparison between Pr-BSC and Pr-B on brain (all subjects and sessions considered). The graphs on the left show the correlation graphs, with T1_Pr-BSC and T1_Pr-SC having a Pearson correlation coefficient of 0.88 (R^2 =0.78) and T1_Pr-BSC and T1_Pr-B a correlation of 0.99 (R^2 =0.99). On the right, the Bland-Altman plots can be observed along with the biases and Limits of Disagreement (LOA). The Bias±LOA between Pr-BSC and Pr-SC on SC

535 is 25.1±38.8 ms and for Pr-BSC and Pr-B is 4.0±28.1 ms.





537 Figure 7: (a,b) average inter-session COV (for all ROIs and subjects). Optimized Pr-BSC

538 showed a slightly better (non-statistically significant) reproducibility than the other two;

539 however, all three protocols perform very well with regards to reproducibility. On bottom, 540 box and Whisker plots demonstrating COV observed with Pr-BSC in the brain (c), the cord

540 box and Whisker plots demonstrating COV observed with Pr-BSC in the brain (c), the cord 541 (d) and per SC levels (e). The boxplot bars represent the minimum, the first quartile (25%),

the median, the mean (shown with X mark), the third quartile (75%) and the maximum from

543 bottom to top, respectively. The highest COV (lowest reproducibility) was observed on the C7

544 level of SC (for one subject and session) and was lower than 3%.