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

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

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40 Research Agency (ANR).

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44	<b>Abbreviations</b>
45	MP2RAGE: Magnetization Prepared 2 Rapid Acquisition Gradient Echo
46	TI1/TI2: First and second inversion times
47	$\alpha_1/\alpha_2$ : 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

72 Magnetization Prepared 2 Rapid Acquisition Gradient Echo (MP2RAGE) is a  $T_1$  mapping  
73 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  
77 specific investigation. This implies large spatial coverage with high spatial resolution and  
78 short acquisition time, high CNR and low  $B_1^+$  sensitivity, as well as high reproducibility and  
79 robust post-processing tools for  $T_1$  quantification in different regions of brain and SC.

80 In this work, a dedicated protocol (referred to as Pr-BSC) has been optimized for  
81 simultaneous brain and cSC  $T_1$  MP2RAGE acquisition at 3T. After computer simulation  
82 optimization, the protocol was applied for in vivo validation experiments and compared to  
83 previously published state of the art protocols focusing on either the brain (Pr-B) or the cSC  
84 (Pr-SC). Reproducibility and in-ROI standard deviations were assessed on healthy volunteers  
85 in the perspective of future clinical use.

86 The mean  $T_1$  values, obtained by the Pr-BSC, in brain white, gray and deep gray matters  
87 were: (mean  $\pm$  in-ROI SD) 792 $\pm$ 27 ms, 1339 $\pm$ 139 ms and 1136 $\pm$ 88 ms, respectively. In cSC,  
88  $T_1$  values for white matter corticospinal, posterior sensory, lateral sensory and  
89 rubro/reticulospinal tracts were 902 $\pm$ 41 ms, 920 $\pm$ 35 ms, 903 $\pm$ 46 ms, 891 $\pm$ 41 ms,  
90 respectively, and 954 $\pm$ 32 ms for anterior and intermediate gray matter. The Pr-BSC protocol  
91 showed excellent agreement with previously proposed Pr-B on brain and Pr-SC on cSC, with  
92 very high inter-scan reproducibility (coefficients of variation of 0.52 $\pm$ 0.36% and 1.12 $\pm$ 0.62%  
93 on brain and cSC, respectively).

94 This optimized protocol covering both brain and cSC with a sub-millimetric isotropic spatial  
95 resolution in one acquisition of less than 8 minutes, opens up great perspectives for clinical  
96 applications focusing on degenerative tissue such as encountered in MS and ALS.

97

98 **Keywords**

99  $T_1$  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  
110 Inversion Recovery (SE-IR) remains the gold standard; but it is not very practical for clinical  
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  
113 suffer from geometrical distortions caused by the static magnetic field inhomogeneities,  
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  $T_1$  quantitative mapping could be  
117 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  
121 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.

133 The MP2RAGE technique was previously optimized for brain investigation at 3T [13] and 7T  
134 [28] based on CNR and limitation of  $B_1^+$  sensitivity, hence providing “standard protocols” for  
135 brain applications. More recently, Rasoanandrianina et al. considered the  $T_1$  values observed  
136 on cervical SC GM and WM and proposed a protocol for imaging cervical SC  
137 specifically [21]. Since the tissue constraints are not the same for brain and cSC, these  
138 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  $T_1$ s 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  $T_1$  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.  $T_1$  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.

148

## 149 2 Materials & Methods

150

### 151 2.1 Simulation

152 Simulations mainly focused on CNR and sensitivity to  $B_1^+$ , considering a 3D isotropic  
153 acquisition allowing to cover both brain and cSC (sagittal orientation preferred here) with a  
154 sub-millimetric resolution (0.9 mm here). Simulation were performed by varying the main  
155 parameters that determine the unique relationship between the UNI image and the  $T_1$  map  
156 [12]. The MP2RAGE repetition time (MP2RAGE TR) was varied between 4000 and 6000 ms  
157 using a 250 ms step. The number of excitations per RAGE module was set to 176 (required  
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 ( $T_{I1}/T_{I2}$ ) were then varied in steps of 50 ms. First and  
160 second RAGE flip angles ( $\alpha_1/\alpha_2$ ) varied from  $3^\circ$  to  $15^\circ$ . The five main parameters which are  
161 MP2RAGE TR,  $T_{I1}/T_{I2}$  and  $\alpha_1/\alpha_2$  were varied and CNR and signal variation with  $B_1^+$   
162 inhomogeneity were investigated at the same time.

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

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

$$172 \text{CNR}_{\text{tissue1VsTissue2}} = \frac{\text{MP2RAGE}_{\text{tissue1}} - \text{MP2RAGE}_{\text{tissue2}}}{\sqrt{\sigma_{\text{tissue1}}^2 + \sigma_{\text{tissue2}}^2}} \cdot \frac{1}{\sqrt{\text{MP2RAGE}_{\text{TR}}}} \quad (1),$$

173 with

$$174 \sigma_{\text{tissue}} = a \sqrt{\frac{(\text{GRE}_{T_{I1}}^2 - \text{GRE}_{T_{I2}}^2)^2}{(\text{GRE}_{T_{I1}}^2 + \text{GRE}_{T_{I2}}^2)^3}} \quad (2),$$

175 with  $\text{MP2RAGE}_{\text{tissue1}}$  and  $\text{MP2RAGE}_{\text{tissue2}}$  the UNI signal in tissue 1 and tissue 2  
176 respectively,  $\sigma_{\text{tissue1}}$  and  $\sigma_{\text{tissue2}}$  the noise propagation in tissue 1 and tissue 2, respectively,  
177  $\text{GRE}_{T_{I1}}$  and  $\text{GRE}_{T_{I2}}$  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:

$$184 \text{CNR} = \text{CNR}_{\text{GMvsWM}} \cdot \text{CNR}_{\text{WMvsCSF}} \quad (3)$$

185 Finally, a  $B_1^+$  map obtained and averaged from 3 healthy volunteers (same volunteers used  
186 later on for in-vivo experiments) was used to determine representative  $B_1^+$  variations  
187 encountered in brain and cSC. As seen on Figure 1, in regions with the highest field  
188 inhomogeneities such as brainstem and cerebral cortex on brain, and C1 and C7 on the cord, a  
189  $B_1^+$  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 ( $\alpha_1/\alpha_2$ ,  $TI_1$ ,  $TI_2$ , MP2RAGE TR) leading to a non-bijective behavior in  
193 lower and upper  $T_1$  boundaries (500 ms and 3000 ms) were removed.

194 Figure 2 shows the simulated relationship between the UNI signal and the  $T_1$  values in  
195 normal conditions and under  $\pm 20\%$   $B_1^+$  variations for 4 different protocols. The first one (fig.  
196 2a), with  $TI_1/TI_2 = 800/3500$  ms;  $\alpha_1/\alpha_2 = 6/3$ ; and MP2RAGE TR = 4750 ms, which  
197 was named Pr-max, provided the highest simulated CNR, at the expense of acquisition time  
198 (9.2 minutes). The second protocol (fig. 2b),  $TI_1/TI_2 = 650/3150$  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  
203 signal in relation with different  $T_1$ s (in optimal  $B_1^+$  condition) for each protocol. This figure  
204 shows the ability and performance of each protocol in tissue discrimination. Given its CNR  
205 and acquisition time, Pr-BSC was kept for subsequent in vivo studies

206

207

208

## 209 **2.2 In-vivo experiment**

210 Protocols Pr-BSC, Pr-SC and Pr-B were tested on healthy volunteers. Sequence parameters  
211 for each protocol are provided in table 1. Data were acquired on a 3T Siemens Verio scanner  
212 with 12-channel head and 4-channel neck coils (Siemens Healthineers, Erlangen, Germany).  
213 Three healthy volunteers (27, 37, 45 years old, 1M/2F) were scanned in three separate  
214 sessions with each protocol, to assess the inter-session reproducibility of each sequence. The  
215 local ethics committee of our institution approved all experimental procedures of the study,  
216 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.

219 The complete post-processing pipeline used to extract metrics in different brain and cSC  
220 ROIs is shown in Figure 4. The first step consisted of the  $B_1^+$  correction of the individual  
221 quantitative  $T_1$  maps using a 3D look-up table (LUT) providing relationship between UNI  
222 and  $T_1$  values in the presence of  $B_1^+$  variation. Then on brain, after anterior-posterior  
223 commissure (AC-PC) alignment of images [31], the UNI-denoised image (provided by the  
224 scanner) was used for segmentation 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  
226 structures (including Nucleus caudate, Putamen and Thalamus) with FSL-FIRST  
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,  
231 which is an unbiased multimodal MRI template of the SC and brainstem [38]. For  $T_1$   
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.

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

241

242

### 243 3 Results

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

247 To transpose the results of simulation, the CNR per unit time for in-vivo data was calculated  
248 from the previously defined formulae (1), using the average and the SD of the UNI signal in a  
249 tissue as  $MP2RAGE_{tissue}$  and  $\sigma_{tissue}$ , respectively. For the sake of simplicity, a global CNR  
250 for the whole GM/WM in brain for all protocols, and GM/WM and WM/CSF on cSC for Pr-  
251 SC and Pr-BSC on each subject was calculated, and the results are summarized in table 2.  
252 The optimized Pr-BSC provided higher CNR for each subject in both brain and cSC.

253 Figure 6 shows the  $T_1$  comparison between Pr-BSC and Pr-SC on cSC (fig. 6a) and Pr-BSC  
254 and Pr-B on brain (fig. 6b). An excellent agreement was seen on brain with a Pearson  
255 correlation coefficient of 0.99 and a Bias $\pm$ LOA (Limits of Agreement)=4.0 $\pm$ 28.1 ms. On SC,  
256 this correlation was found equal to 0.88 with a Bias $\pm$ LOA=25.1 $\pm$ 38.8 ms. It should be noted  
257 that the bias on SC is lower than the mean in-ROI SD observed in cSC (around 39 ms).

258 The average  $T_1$  values found with Pr-BSC on different regions of WM and GM on brain and  
259 cSC are summarized in table 3, together with values reported previously in the literature. The  
260 mean  $T_1$  values observed with our optimized Pr-BSC in brain WM, GM and deep GM were  
261 792 $\pm$ 27 ms, 1339 $\pm$ 139 ms and 1136 $\pm$ 88ms, respectively. In the cSC, the values for WM  
262 corticospinal (CST), posterior sensory (PST), lateral sensory (LST) and rubrospinal &  
263 reticulospinal (RST) tracts were 902 $\pm$ 41 ms, 920 $\pm$ 35 ms, 903 $\pm$ 46 ms, 891 $\pm$ 41 ms,  
264 respectively, and 954 $\pm$ 32ms for anterior & intermediate GM. No statistically significant  
265 differences were observed between different cervical levels. Inter-subject, in-ROI and inter-  
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%.

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

272

### 273 4 Discussion

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

277 The optimized Pr-BSC showed excellent agreement with the  $T_1$  values obtained with the  
278 standard brain protocol (Pr-B) in all ROIs [13], [16]. On cSC, a small bias (25 ms,



279 representing 2.8% of the mean T<sub>1</sub>) was observed as compared to the reference protocol [21],  
280 which represents less than the average cSC in-ROI SD and was therefore not further  
281 investigated.

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

285

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<sub>1</sub> 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 T<sub>1</sub> 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

297 Pr-BSC also provides an increased CNR as compared to Pr-B, which was initially optimized  
298 for both CNR and B<sub>1</sub><sup>+</sup> immunity. Here, CNR gain optimization made for Pr-BSC comes at an  
299 expense of B<sub>1</sub><sup>+</sup> immunity and further necessitates a B<sub>1</sub><sup>+</sup> correction strategy (as previously  
300 proposed by Massire et al. [20]). The different coil set ups (12+4 channel head and neck here,  
301 as compared to optimal 32 channel in the original study [13], [16]) may also have slightly  
302 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.

312

313

## 314 **5 Conclusion**

315

316 This work proposes an optimized protocol dedicated to sub-millimetric simultaneous brain  
317 and cSC T<sub>1</sub> MP2RAGE mapping at 3T, compatible with clinical scan time.

318

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

323

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338

339 **References**

340

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451

452

453 **Tables**

454

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

	TI1/TI2	$\alpha_1/\alpha_2$	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

456

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*  
460 *cover the entire cervical cord so CNR for SC GM/WM was not calculated in that case. The*  
461 *optimized Pr-BSC provided the highest CNR on each subject and on average for brain and*  
462 *cSC, separately. Please note that the coil set-up used here (12+4 channels for brain and cSC)*  
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

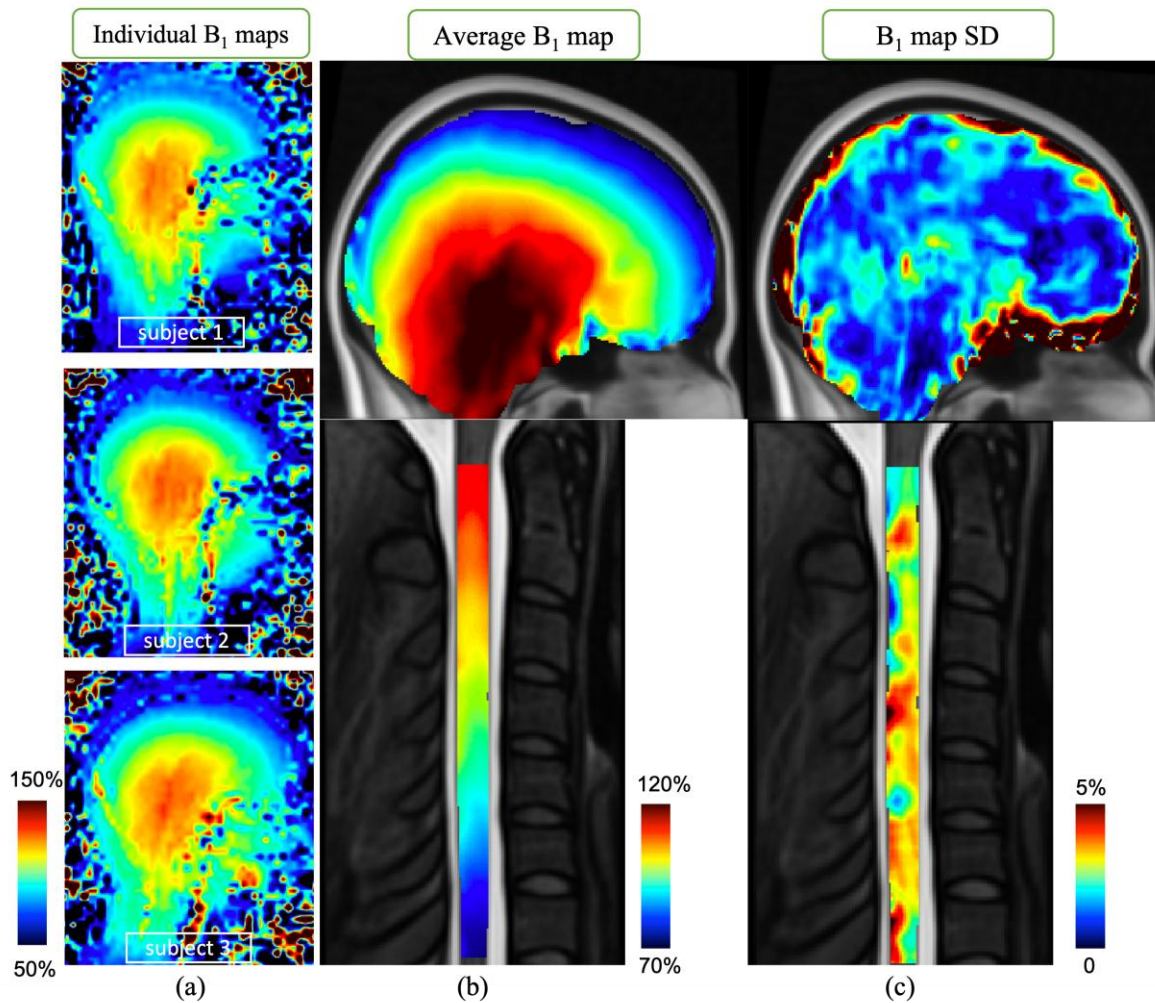
	CNR for brain GM/WM			CNR for SC GM/WM		CNR for SC WM/CSF	
	<b>Pr-BSC</b>	Pr-B	Pr-SC	<b>Pr-BSC</b>	Pr-SC	<b>Pr-BSC</b>	Pr-SC
Sub 1	<b>1.75</b>	1.45	1.60	<b>0.27</b>	0.23	<b>3.14</b>	2.50
Sub 2	<b>1.67</b>	1.46	1.61	<b>0.29</b>	0.27	<b>2.82</b>	2.64
Sub 3	<b>1.57</b>	1.46	1.51	<b>0.29</b>	0.28	<b>3.90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

467

468 *Table 3: Average  $T_1$  values (in ms) obtained with Pr-BSC in this study on brain and SC and*  
469 *comparison with values reported in previous studies either on the brain or the cord. For this*  
470 *study, the standard deviations (in ms) are reported for inter-subject, in-ROI and inter-session*  
471 *(mean of the individual inter-session SD). The inter-session SD is the lowest SD in all regions*  
472 *(in this study), which shows a great robustness for the technique. For the other studies cited*  
473 *in the table, the SD represents the inter-subject variation. A good agreement with previously*  
474 *reported  $T_1$  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.*

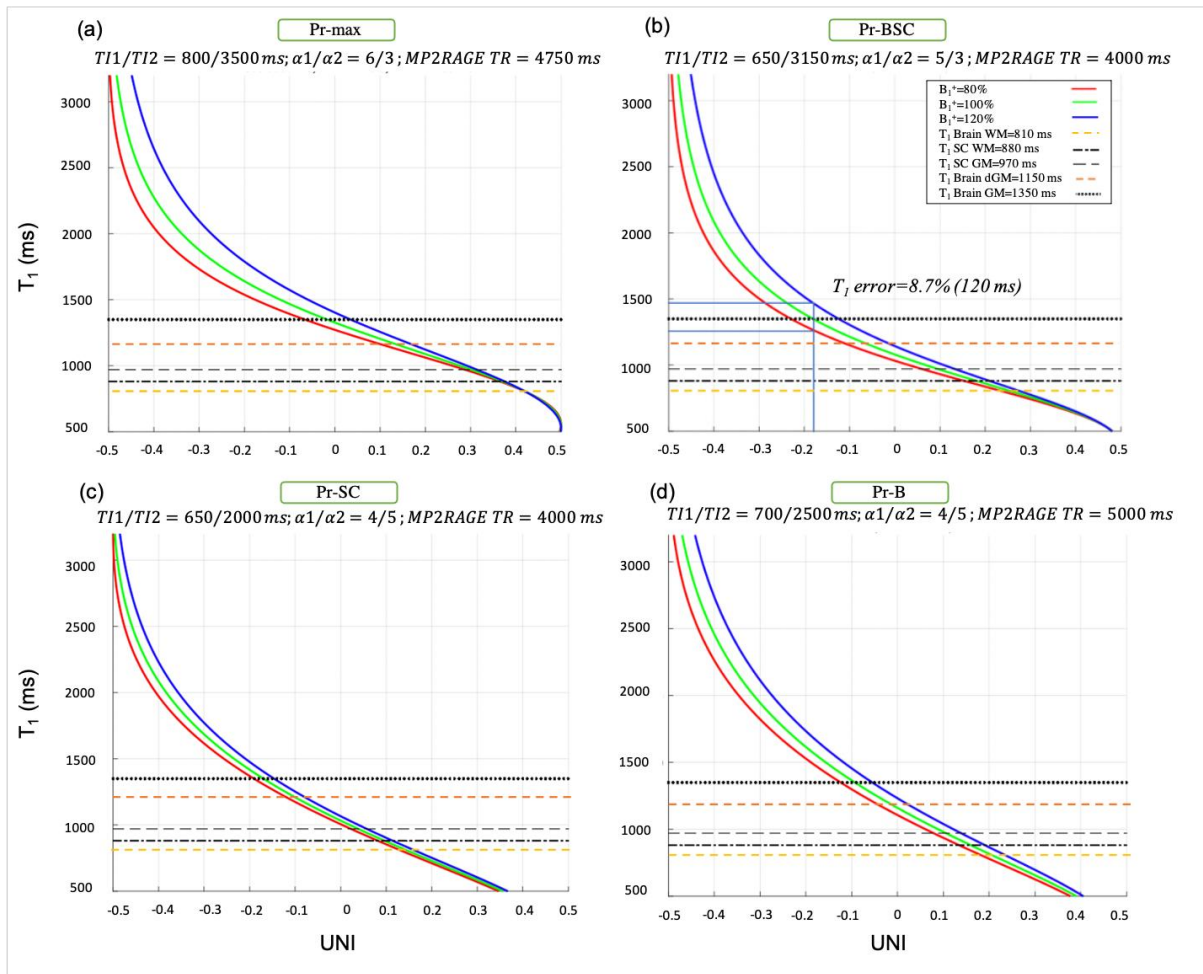
Brain						
This study (mean±[inter-subject SD; ROI SD; inter-session SD])			Marques 2010 [12] (MP2RAGE)	Wright 2008 [40] (MPRAGE)	Okubo 2015 [14] (MP2RAGE)	
WM	Frontal	787±[15;23;2]	810±30	840±50	-	
	Parietal	794±[8;23;2]				
	Occipital	790±[10;30;2]				
	Temporal	797±[8;34;2]				
GM	Frontal	1312±[57;139;10]	1350±50	1610±100		
	Parietal	1322±[50;136;11]				
	Occipital	1318±[31;139;9]				
	Temporal	1407±[50;135;10]				
Deep GM	Caudate	1206±[18;65;6]	1250±70	1390±50		1217±30
	Putamen	1151±[51;84;4]	1130±70	1330±70		1095±31
	Thalamus	1053±[22;115;7]	1080±70	-	1077±30	
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)	
WM	CST	902±[18;41;10]	877±35	876±27	-	
	PST	920±[28;35;10]	920±37		-	
	LST	903±[34;46;9]	-		1110±83	
	RST	891±[25;41;9]	-			
GM	Anterior & Intermediate	954±[35;32;10]	934±33	973±33	1136±90	





480

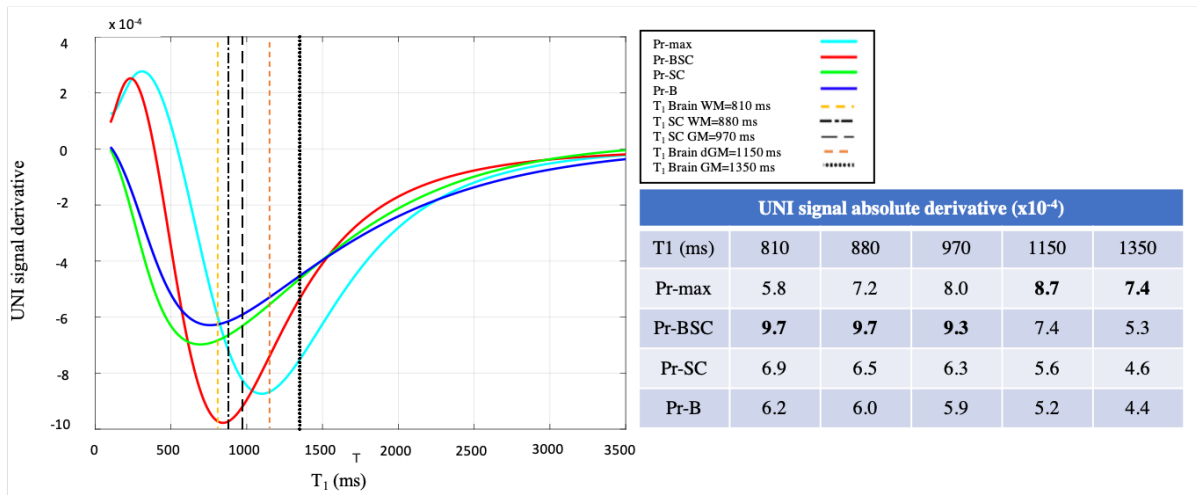
481 *Figure 1: (a) Individual  $B_1^+$  maps acquired with preconditioning RF pulse with*  
 482 *TurboFLASH Readout [30] on 3 healthy subjects. (b) Mean and (c) standard deviation of  $B_1^+$*   
 483 *maps over 3 healthy subjects, presented in the ICBM MNI-152 [35], [36] and PAM50 [38]*  
 484 *spaces. It can be observed in (b) that the highest  $B_1^+$  field inhomogeneities can be observed*  
 485 *in brainstem and cerebral cortex on brain, and C1 and C7 on the cord and in these regions, a*  
 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.*



489

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.*

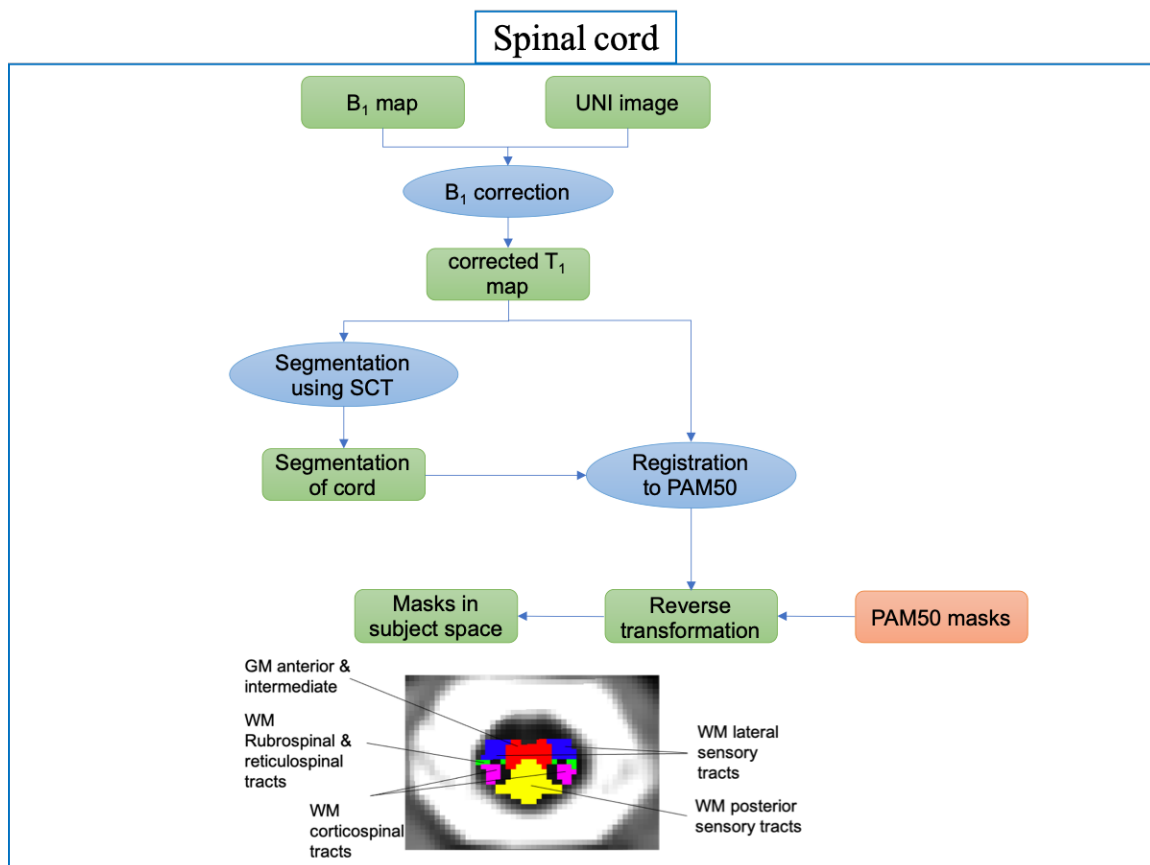
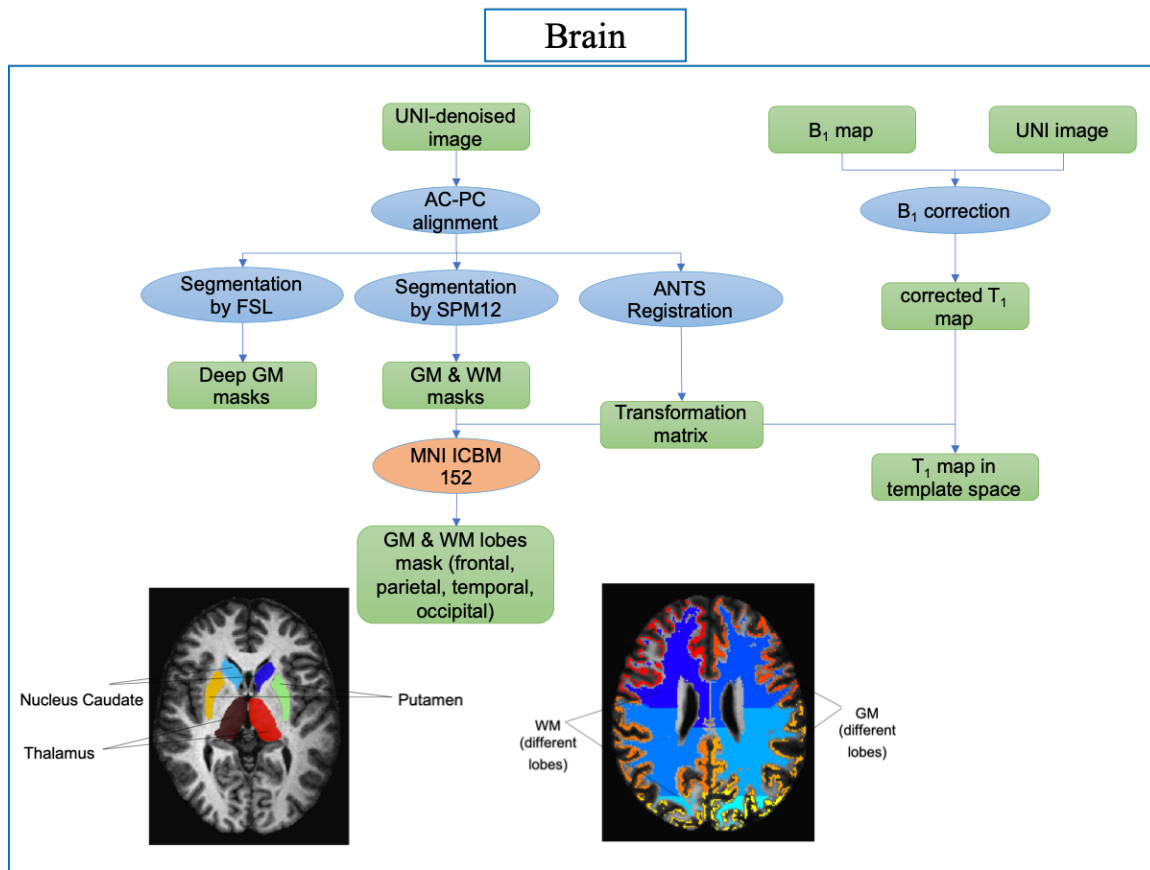
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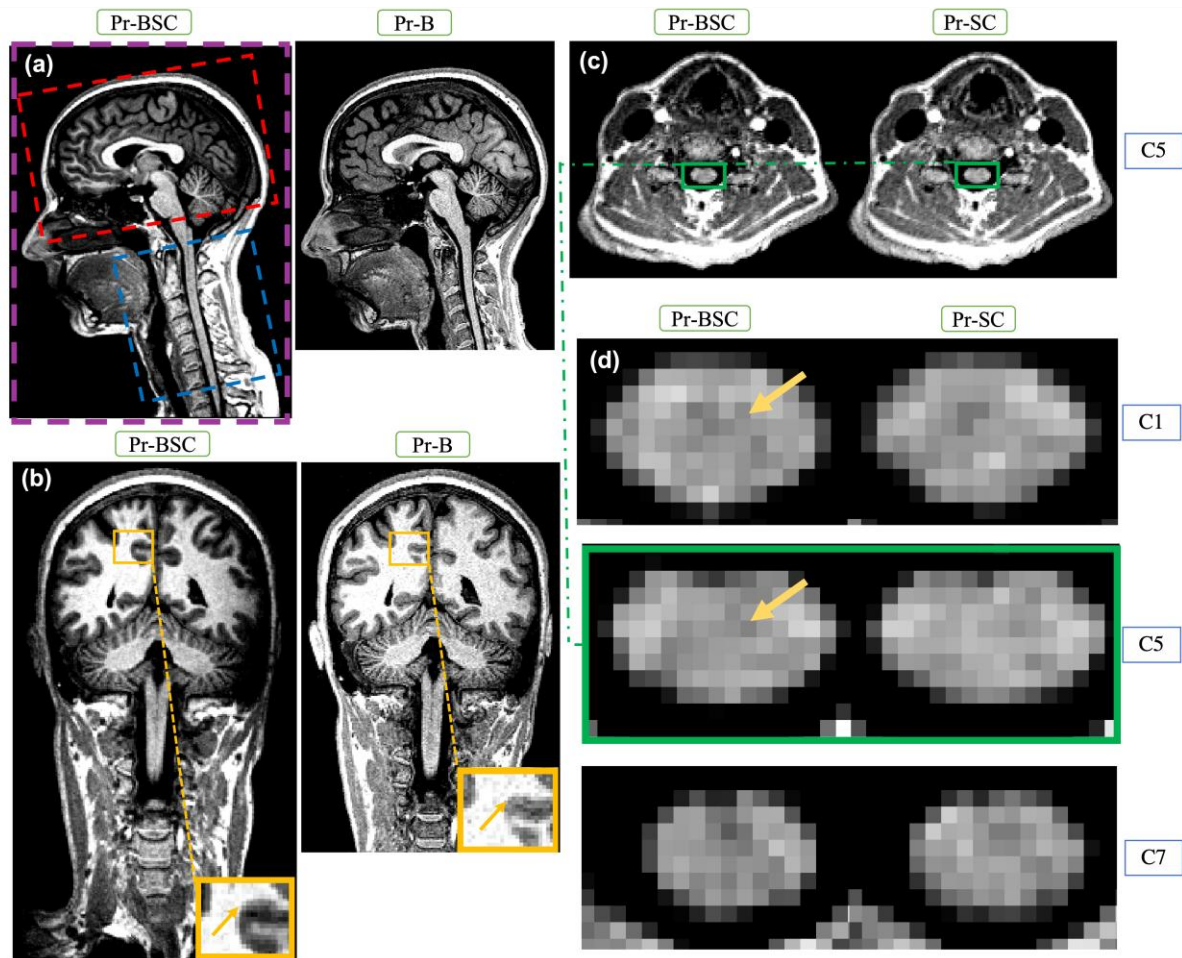
504 *Figure 3: (left) Derivative of the UNI signal along  $T_1$  values (slope of the graphs in figure 2)*  
 505 *; this graph provides indications on the specificity of each protocol and their performance in*  
 506 *discriminating between different tissues. The table (right) summarizes the absolute of that*  
 507 *signal derivative for different  $T_1$ s found in brain and cSC tissues. For  $T_1$ s < 1040 ms, Pr-BSC*  
 508 *shows the highest (absolute) values and for  $T_1$ s > 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*  
 511 *at the expense of a lower  $B_1^+$  immunity which necessitates the implementation of a  $B_1^+$*   
 512 *correction strategy to avoid  $T_1$  estimation biases.*

513



514

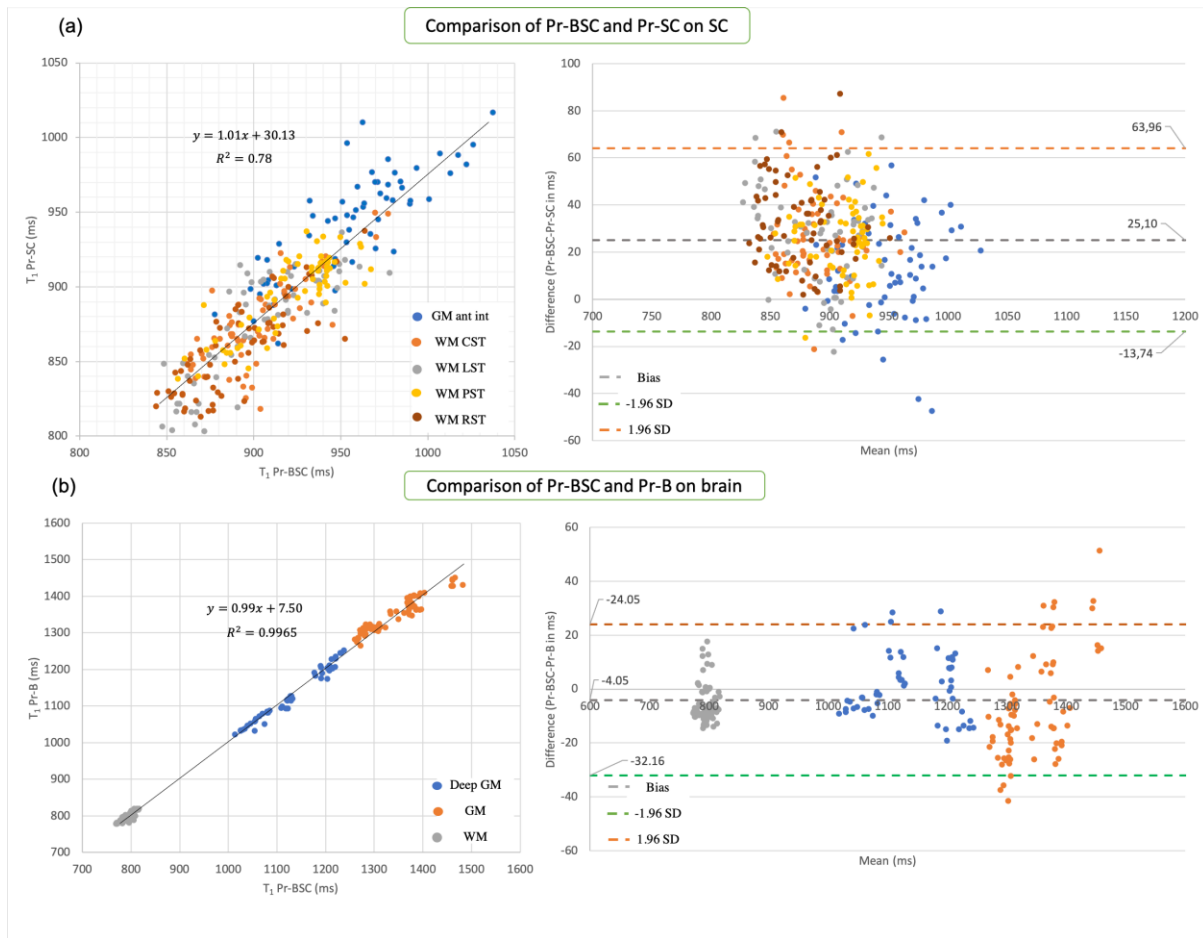
515 *Figure 4: Post-processing steps for brain and cSC, with indication of the main regions of*  
 516 *interest.*



517

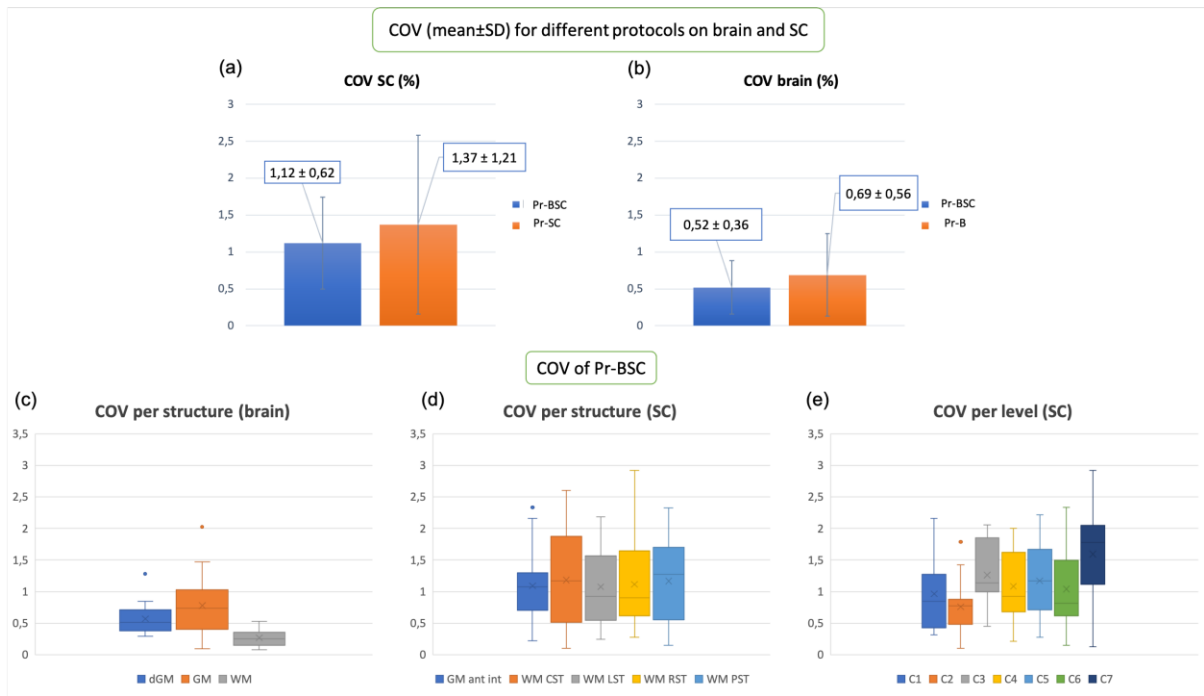
518 *Figure 5: (a) Representation of UNI-denoised image (no unit) for Pr-BSC (FOV 315x262*  
 519 *mm<sup>2</sup>) and Pr-B (FOV 256x240 mm<sup>2</sup>) on brain in sagittal and (b) coronal views. (c)*  
 520 *Representation of UNI-denoised image for Pr-BSC and Pr-SC in the axial plane at the C5*  
 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*  
 523 *the volume of interest in previous cSC studies [21], [22] and the purple box shows how Pr-*  
 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.*

527



528

529 *Figure 6: (a) comparison between Pr-BSC and Pr-SC on different ROIs of cSC; (b)*  
 530 *comparison between Pr-BSC and Pr-B on brain (all subjects and sessions considered). The*  
 531 *graphs on the left show the correlation graphs, with  $T_1$  Pr-BSC and  $T_1$  Pr-SC having a*  
 532 *Pearson correlation coefficient of 0.88 ( $R^2=0.78$ ) and  $T_1$  Pr-BSC and  $T_1$  Pr-B a correlation*  
 533 *of 0.99 ( $R^2=0.99$ ). On the right, the Bland-Altman plots can be observed along with the*  
 534 *biases and Limits of Disagreement (LOA). The Bias $\pm$ LOA between Pr-BSC and Pr-SC on SC*  
 535 *is 25.1 $\pm$ 38.8 ms and for Pr-BSC and Pr-B is 4.0 $\pm$ 28.1 ms.*



536

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*  
 541 *(d) and per SC levels (e). The boxplot bars represent the minimum, the first quartile (25%),*  
 542 *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%.*

545