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**Title:** Simultaneous brain and cervical spinal cord MP2RAGE for T1 measurement: robustness and sensitivity for tissue modification assessment in multiple sclerosis in a multicenter context

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## Introduction

Recent optimisations of T1 quantification through magnetization-prepared two rapid acquisition gradient echoes (MP2RAGE; Marques et al. 2010) allow to perform both brain and cervical spinal cord acquisitions simultaneously with good trade-off between acquisition time, robustness and accuracy (Rasoanandrianina et al. 2019; Forodighasemabadi et al. 2021). This sequence is of particular interest to investigate tissue microstructural modifications in pathologies such as multiple sclerosis (MS) (Demortière et al. 2020; Mchinda et al, 2021). In order to spread out the use of the MP2RAGE sequence, we evaluated the reproducibility and variability in two different centres.

## Methods

The data included in this work were collected in the context of the multicentric MSTRACTS (NCT04220814), OSV-IRM (NCT05107232) and T1-M3C-SEP (FLI-RE2) studies. Six healthy controls (HC; F/M: 4/2, mean age 38.9 years) were scanned 3 times each (separated sessions), in two different centres both equipped with 3T Siemens scanners (Prisma with 20 channels in centre 1, Vida with 64 channels in centre 2 ). Additionally 26 HC (centre 1/2: 20/6) were scanned one time (F/M: 19/7, mean age 39.2 years). The same acquisition protocol was performed in both centres and included MP2RAGE and B1 map acquisitions covering both brain and cervical spinal cord (cSC). The acquisition parameters were previously described in (Rasoanandrianina et al. 2019; 4000ms TR, 243×300mm<sup>2</sup> FOV, 176 slabs, 6/8 partial Fourier (PF) factor 0.9×0.9×1mm<sup>3</sup> voxel size, TI1/TI2 = 650/2000ms,  $\alpha_1/\alpha_2=4/5^\circ$ , GRAPPA 2). After B1 correction (Massire et al. 2016), mean T1 values were extracted in different regions including brain white matter (bWM), deep grey matter (dGM) and cortical grey matter (cGM; all computed using CAT12 [(Ashburner and Friston 2000)]) and all cSC segments (computed using the SCT toolbox [(De Leener et al. 2017)]). We evaluated the variability between centres and subjects using linear mixed-effects models with subject as random effect and centre as fixed effect. The coefficients of variation (CV)

and the intraclass correlations (ICC) of between-session and between-participant variabilities were computed according to Combès et al. (2019). In order to interpret these results with respect to potential application in MS pathology, we also reported exploratory analyses based on the extraction of T1 values in the same regions for 5 MS patients (centre 1/2: 3/2, same acquisition protocol and image processing) without cSC lesions.

## Results

For the whole dataset collected in HC, the mean (and standard deviation) T1 values in the brain were 1281.5 (28.8), 1176.5 (20) and 823.9 (21.1) ms for cGM, dGM, and bWM, respectively and were ranging from 921 (22.6) to 954 (30.5) ms over the 7 cSC segments (see Fig. 1)

For the brain, we observed evidence of centre differences for the three regions (all  $p < .01$ ). Nevertheless, the estimated differences between centres were low, ranging from 4.71 (bWM) to 25.31 (dGM) ms (ie. 0.57 to 1.98% of the mean). Between-participant CV were 2.1, 1.7 and 1.8%, and between-session CV were 0.2, 2.2 and 0.5% for bWM cGM and dGM, respectively. Between-session ICC were .01, .61 and .06 for the same regions.

For the SC, we observed evidence of centre differences for all vertebrae (all  $p < .05$ ), except C4, C5 and C7 ( $p = .149, .163, .062$ , resp.). The estimated mean differences were also low, ranging from 9.6 (C5) to 20.2 (C1) ms (ie. 1.03 to 2.15%). To simplify the results, T1 values from C3 to C5 levels were averaged. In this region, between-participant and between-session CV were 1.5 and 1.6%, while between-session ICC was .53.

MS patients showed a mean T1 value increase ranging from 19.5 (cGM) to 44.2 (dGM) ms for the brain, and from 14 (C7) to 122.7 (C3) ms for the cSC compared to the mean in all HC. Fig. 2 shows that, for each region, the majority of patients (coloured triangles) have higher T1 values than the third quartile of HC.

## Discussion

Our results showed that, even if differences exist between the two centres, the variability is low, especially for bWM (0.57 %) and central cSC segments (1.03 %). Moreover, the T1 variability is primarily explained by between-participant variability for the brain and by both session- and participant-variabilities for cSC. The differences between scanners were found to be less important than the differences observed between HC and MS patients with no cSC lesions. Overall, our results highlight the multicenter robustness of simultaneous brain and cervical spinal cord acquisition and its potential for further applications in multicenter MS studies to assess regional tissue impairment.

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## Figures

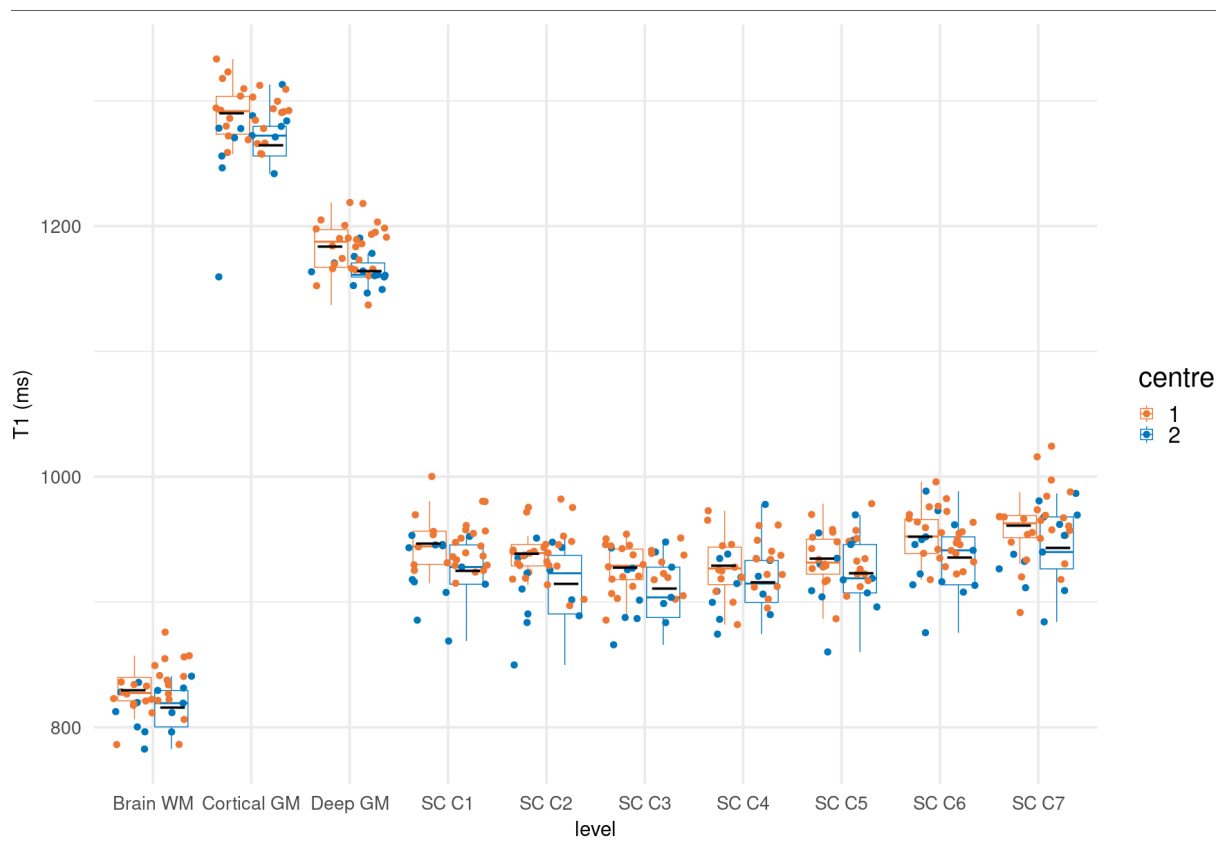


Figure 1: Mean T1 values for all healthy controls grouped by centre (Centre 1 in orange, Centre 2 in blue) for the regions of interest located in the brain and the cervical spinal cord. Boxplots display the median, the first and third quartiles. Black bars display the mean of all healthy controls for each centre and each region. Legend: WM=white matter; GM=grey matter; SC=spinal cord; ms=millisecond.

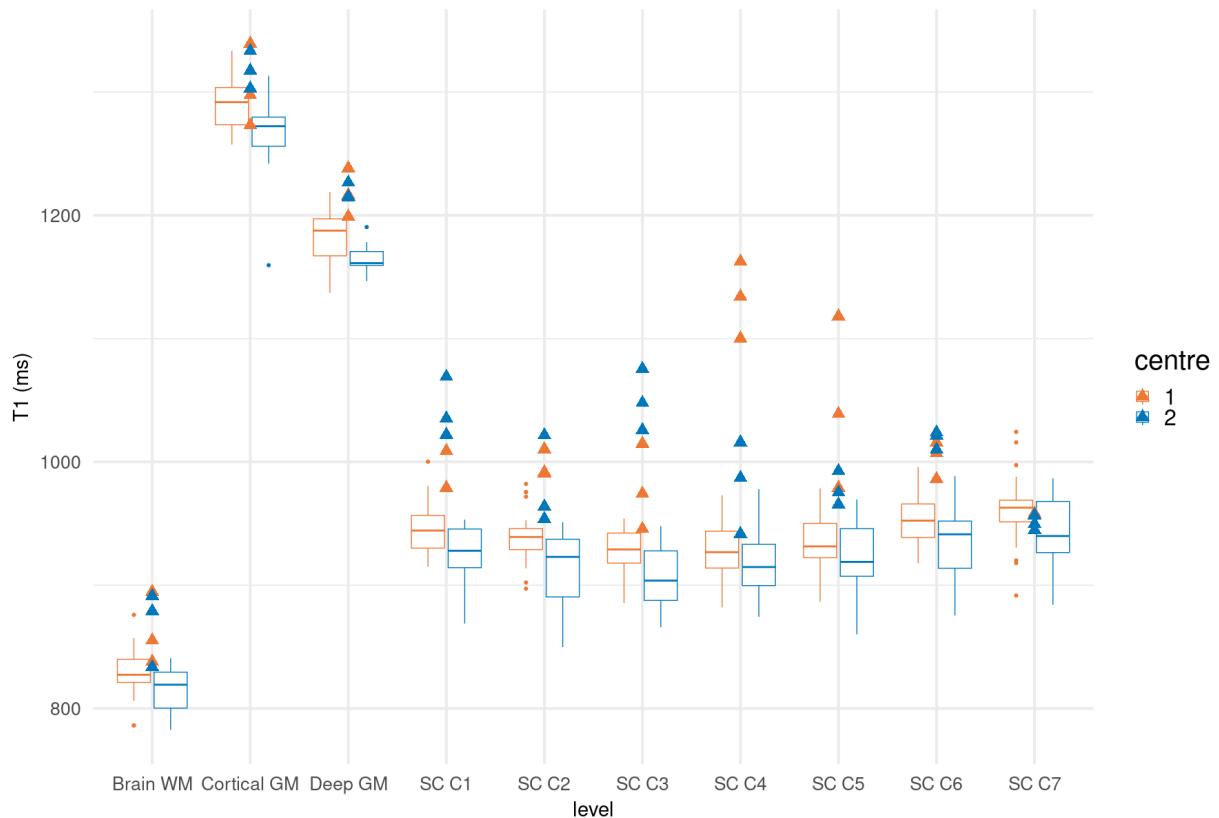


Figure 2: Mean T1 values for all healthy controls grouped by centre (Centre 1 in orange, Centre 2 in blue) and the 5 MS patients for the regions of interest located in the brain and the cervical spinal cord. Boxplots display the median, the first and third quartiles in the HC group. Triangles represent the mean signal for each MS patient. Dots represent outliers for healthy controls. Legend: WM=white matter; GM=grey matter; SC=spinal cord; ms=millisecond.

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