A multi-center study on fast full-brain quantitative multi-parameter mapping of R1, MT, and R2*: scan-rescan repeatability and inter-site reproducibility

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Synopsis

We present a multi-center, multi-vendor study evaluating repeatability and reproducibility of quantitative MRI data acquired using high resolution (1 mm³) multi-parameter mapping which provides quantitative R1, MT and R2* maps of the whole brain within less than 18 min. The protocol was implemented at four clinical sites with different Siemens and Philips 3T MRI scanners. Scan-rescan measurements of the same five healthy volunteers at all sites showed good intra-site reproducibility in all parameter maps. However, the inter-site comparisons showed higher reproducibility within a single vendor than across vendors.

Background

Quantitative MRI (qMRI) aims to provide imaging biomarkers that are insensitive to differences in MR soft- and hardware[1]. Now studies are increasingly conducted at multiple sites to raise the number and diversity of the participants and investigate rare diseases using MRI technology[2]. However, standardized MRI methods that produce stable results across different scanners in longitudinal studies are still needed[3]. The multi-parameter mapping (MPM) approach[4,5] provides high resolution maps sensitive to myelination (MT and R1) and iron content (R2*) in the brain and has been already applied in a wide range of studies to investigate microstructural tissue properties in WM and GM and its potential for providing biomarkers [2,6,7]. Our previous multi-center study with the MPM approach, using the same MRI scanner (Siemens Trio-VB17), showed reproducibility of the quantitative maps for multi-center imaging studies[2]. Therefore, MPM will be applied in an European multi-center clinical trial (NISCI) on investigating a drug effect based on the Anti Nogo-A antibody[8] (the treatment facilitates neuro-generation at the anatomical level in spinal cord injury) and implemented with the vendor's product MRI sequences. For a validation at each site involved in the NISCI trial, we aimed to investigate scan-rescan repeatability and inter-site reproducibility of the MPM with changing scanner conditions (different vendors) and repositioning subjects for scan-rescan repeatability.

Materials and Methods

The same 5 healthy controls (2 females, age=32.4±6.0 years) were scanned twice (scan-rescan) with about 1 hour break in between on four different scanners at four centers in Switzerland, Germany, Italy, and Spain (Table 1a). The study received ethics approval at each center. The MPM comprised three multi-echo 3D FLASH scans designed to provide MR parameter measures of longitudinal relaxation rate (R1=1/T1), magnetization transfer saturation (MT), and effective transverse relaxation rate (R2*=1/T2*)[4,5] with the parameters listed in Table 1b. The post-processing was done by using the hMRI toolbox (www.hmri.info), implementing voxel-based quantification (VBQ)[9] to create maps of MT, R1 (using UNICORT[5]) and R2* (using ESTATICS[10]). Mean MT, R1 and R2* within WM and GM were derived from the corresponding maps. Scan-rescan repeatability was assessed by determining the absolute value of the difference between scan and rescan values per subject, divided by the mean of both measurements. Coefficient of variance (CoV) within and between sites was calculated to determine intra- and inter-site reproducibility[2] for each parameter.

Results

The MPM protocol provided high quality parameter maps (Fig. 1). The mean R1, R2* and MT in GM and WM across sites and subjects are presented in Table 2a. The results of scan-rescan repeatability per site, inter- and intra-site CoV for MT, R1 & R2* are shown in Tables 2b,c,d. The scan-rescan repeatability was higher on Siemens scanners than those calculated on the Philips scanner – especially for MT and R1 maps (Fig. 2). The intra-site CoVs were less than 2% for R2* and less than 5% for MT. However, the intra-site comparison showed a higher variation (<8%) for R1 in both GM and WM. The inter-site CoVs were less than 5% for all parameters across sites with Siemens scanners. However, inter-site CoVs of parameters determined across all sites including Philips scanner showed higher CoVs (<20%).

Discussion and Conclusion

This multi-center multi-vendor validation showed a high scan-rescan repeatability and intra-site reproducibility of the MPM approach based on product sequences compared to conventional T1w method[2]. The high scan-rescan repeatability promises high sensitivity in longitudinal studies. While the mean R1 and R2* values were in agreement with previous reports[2], the mean MT was slightly higher, which is in line with applying more highly powered MT saturation pulses than in the previous report[2]. Moreover, the Philips scanner has different MT saturation pulse settings compared to Siemens, leading to systematic differences in MT values between the vendors. The observed higher CoVs within subjects for R1 in both WM and GM may be due to higher sensitivity of R1 to the transmit radio-frequency (RF) amplitude. Despite using different Siemens scanners with different software versions as well as different RF coils across sites, we obtained high scan-rescan repeatability and intra-site reproducibility of MPM parameters. However, we observed deviations from the Philips scanner results that need to be taken into account when pooling data across sites. In conclusion, our results show that MPM provides high resolution maps in a short acquisition time, promising MR biomarkers with high reproducibility and sensitivity to tissue microstructure needed for multi-center trials.

Acknowledgements

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Figures

a)

	Site Information	Scanner Vendor	Software	RF Coils Channels
Site 1	Clínica Creu Blanca Radiology Department, Barcelona	Siemens 3.0 T (Verio)	VD 13A	32
Site 2	Heidelberg University Hospital, Spinal Cord Injury Center, Heidelberg	Siemens 3.0 T (Verio)	VB 19	16
Site 3	University of Zurich, Spinal Cord Injury Center Balgrist, Zurich	Siemens 3.0 T(SkyraFit)	VE 11B	16
Site 4	Santa Lucia Fondazion, IRCCS, Rehabilitation Hospital, Rome	Philips 3.0T (Achieva)	3.2.3 X-series	16

b)

Acquisition parameter	PDw	MTw	T1w
TR	18 ms	37 ms	18 ms
TE	6 echoes, equidistant between 2.46ms and 14.76ms		
Flip angle	4°	6°	25°
MT pulse	500° (320°)		
GRAPPA factor	2 (SENSE factor 1.25 on Philips scanner)		
Resolution	1 mm, isotropic		
Field of View	256x240mm		
Partial Fourier	6/8 (5/8 on Philips scanner)		

Table 1: a) Scanners and sites involved in this study **b)** Acquisition parameters for multi-parameter mapping on Philips and Siemens scanners.
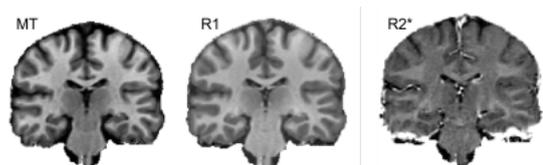

Figure 1: Coronal slices at x=129 for the mean of MT, R1 and R2* maps from one subject, across all sites. Values scaled from black to white (MT: 0-5 p.u.; R1: 0-1.5/s; R2*: 0-50/s)
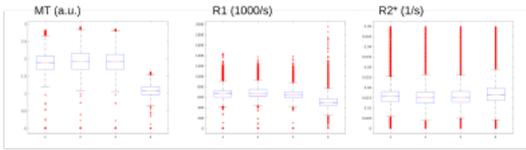
Figure2: Boxplots of voxel wise data for GM segmentations from one subject for all four sites, MT values are scaled. (numbered as in Table 1).

Table 2 (a)

ROI Mean±SD	R1		MT		R2s	
	Across sites (1-3)	Across site 4	Across sites (1-3)	Across site 4	Across sites (1-3)	Across site 4
GM	0.628±0.033	0.422±0.057	1.88±0.057	1.30±0.213	15.8±0.74	16.91±1.1
WM	1.010±0.059	0.691±0.10	3.00±0.134	2.54±0.31	22.01±0.72	22.4±0.92

Table 2 (b)

Test retest repeatability per site [%]	R1	MT	R2*
Site 1 (Siemens 3T Verio)			
GM	3.64	2.98	1.24
WM	4.69	2.32	0.74
Site 2 (Siemens 3T Verio)			
GM	6.51	1.43	1.58
WM	6.74	1.62	1.14
Site 3 (Siemens 3T Skyra)			
GM	4.50	2.18	3.03
WM	3.74	1.83	2.15
Site 4 (Philips 3T Achieva)			
GM	13.02	16.03	3.13
WM	13.28	10.13	1.96

Table 2 (c)

Intra site CoV [%]	R1	MT	R2*
GM	6.07	4.70	1.84
WM	7.19	3.40	1.52

Table 2 (d)

Inter site CoV [%]	R1		MT		R2s	
	Across sites (1-4)	Across sites (1-3)	Across sites (1-4)	Across sites (1-3)	Across sites (1-4)	Across sites (1-3)
GM	19.6	4.2	16.9	2.7	12.6	1.7
WM	19.2	4.5	19.9	2.3	3.9	1.4

Table 2: a) The mean±SD, **b)** test-retest repeatability, and **c,d)** intra and inter site variations of MPM parameters across sites and subjects.