Original Article

Rapid quantification of global brain volumetry and relaxometry in patients with multiple sclerosis using synthetic magnetic resonance imaging

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Background: Early pathologic studies have reported that focal areas of gray lesions in the cortex and other gray matter (GM) regions are important in multiple sclerosis (MS) patients. Quantitative magnetic resonance imaging (qMRI) can provide more specific insight into the disease process, progression, and therapeutic response of MS. The purpose of this study was to quantitatively assess the changes of global GM volumetry and relaxometry information simultaneously in MS patients using synthetic MRI.

Methods: All MS patients and healthy controls (HCs) were recruited. The Expanded Disability Status Scale (EDSS) scores were obtained from all patients to evaluate the disability progression. Volumetry and relaxometry of the global brain and regional GM were obtained. The quantitative parameters between MS patients and HCs were compared using an analysis of covariance (ANCOVA). The Pearson correlation assessed the correlations between the quantitative parameters and EDSS, illness duration, education in MS patients.

Results: Thirty-five MS patients and fifty-two age-matched HCs were enrolled in this prospective case-control study. The global volumetry including white matter volume (WMV), myelin volume (MYV), and brain parenchymal volume (BPV) were all significantly lower in MS patients (WMV: 613.120±65.388 *vs.* 579.903±68.432 mL; MYV: 151.883±22.766 *vs.* 192.457±27.381 mL; BPV: 1,136.771±106.126 *vs.* 1,276.712±107.368 mL), as well as a higher cerebral spinal fluid volume (CSFV) (241.294±81.805 *vs.* 177.017±39.729 mL) in MS patients than those in HCs. Similarly, brain parenchymal fraction (BPF) and myelin fraction (MYF) were significantly lower in MS patients (BPF: 82.623±5.368 *vs.* 87.85±2.392 mL; MYF: 11.034±1.529 *vs.* 13.231±1.465 mL). For regional GM volumetry, multiple regions of MS patients were significantly smaller than those of HCs ($P<0.01$, corrected). For regional GM relaxometry, the T1, T2, and PD values of multiple regions showed significant differences.

Conclusions: These findings suggest that MS patients had global and regional brain volumetry and relaxometry alterations, and the synthetic MRI-derived parameters may be potentially used as specific quantitative markers for the clinic to improve the understanding of MS.

Keywords: Synthetic magnetic resonance imaging (synthetic MRI); multiple sclerosis (MS); global brain volumetry; relaxometry; gray matter (GM)

Submitted Oct 02, 2021. Accepted for publication Mar 07, 2022.
doi: 10.21037/qims-21-970
View this article at: https://dx.doi.org/10.21037/qims-21-970

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Introduction

Multiple sclerosis (MS) is a neurological disease pathologically characterized by demyelination, inflammation, axonal loss, and gliosis scattered throughout the central nervous system (CNS). Clinically, MS is considered primarily a white matter (WM) disease. WM lesion load, as measured by magnetic resonance imaging (MRI), has been used to explain part of the pathological processes (1-3). However, specific cognitive impairments, such as reduced mental processing, attention impairment, and memory deficits, which can be found in 45–65% of MS patients (4-6), might be better explained by physical disability in gray matter (GM) (7,8). Some pathological studies have reported significant foci of GM lesions in the cerebral cortex and other GM regions are of importance (9-11).

Conventional MRI plays an important role in the diagnosis and follow-up of MS patients (12). Quantitative measurements, such as the loss of specific tissue types and global and regional brain atrophy, are gaining increasing attention as critical clinical markers to determine disease severity and prognosis in MS patients (13). Compared with conventional MR imaging techniques, quantitative MR imaging can not only characterize the focal visualized lesions of MS but also detect the hidden abnormalities in normal-appearing gray matter (NAGM) and normal-appearing white matter (NAWM) (14-16).

In the vast majority, only one parameter per scan can be measured using quantitative MR. Synthetic MRI allows simultaneous acquisition of T1, T2 and PD values, and subsequent reconstruction of synthetic images that resemble conventional MR images from a single scan within a clinically time. Importantly, synthetic MRI can automatically segment brain tissue based on the relaxation value and provide volumetry information of different types of brain tissues, including volumes of GM, WM, myelin content, and cerebral spinal fluid (CSF) (17,18). Furthermore, the method offers scanner independence and acceptable scanning times, since a single acquisition can provide data for reconstructing all image sets.

To the best of our knowledge, there are no previous reports of using synthetic MRI to simultaneously explore global and regional GM volumetry and relaxometry information in MS by automatically segmenting brain regions. The purpose of this study was to quantitatively assess the changes of GM volumetry and relaxometry information simultaneously in MS patients using synthetic MRI. We present the following article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-21-970/rc)

Methods

Subjects

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Research Ethics Committee of China Medical University, and informed consent was provided by all participants.

All MS patients and healthy controls (HCs) were recruited at the First Hospital of China Medical University from September 2019 to May 2021. The inclusion criteria for this study were as follows: age between 18 and 65 years; had a clinically definite MS based on revised McDonald's criteria (19); study exclusion criteria were as follows: (I) had received corticosteroid treatment in the last 2 weeks preceding the study (n=3); (II) had the previous history of other CNS's diseases such as demyelinating and neurodegenerative diseases, brain tumor or surgery, head injury, cerebrovascular disease (n=1); (III) had poor image quality (n=3). The age-well matched HC subjects had no history of hypertension, neurological or psychiatric diseases, brain malformations, or trauma based on the conventional MRI. The flowchart of this study was shown in *Figure 1*. Neurological disability was assessed using the Expanded Disability Status Scale (EDSS) within one week after the MRI scan (20).

MRI protocol

MRI images were acquired based on a 3.0 Tesla MR scanner (SIGNA Pioneer, GE Healthcare, Milwaukee, WI, USA) equipped with a standard 21-channel phased-array head-neck coil. Conventional axial T1 and T2-weighted images (T1WI and T2WI), sagittal T1WI, and fluid-attenuated inversion recovery (FLAIR) were obtained to exclude participants with brain lesions.

Synthetic MRI [MAGnetic resonance image Compilation (MAGiC)] images (21) were obtained through the whole head for each subject using multiple-delay-multiple-echo (MDME) sequence: field of view (FOV) =240 mm × 192 mm, in-plane resolution =0.8 mm × 1 mm, matrix =320×192, echo time (TE) 1/TE 2 =17.5 ms/87.7 ms,

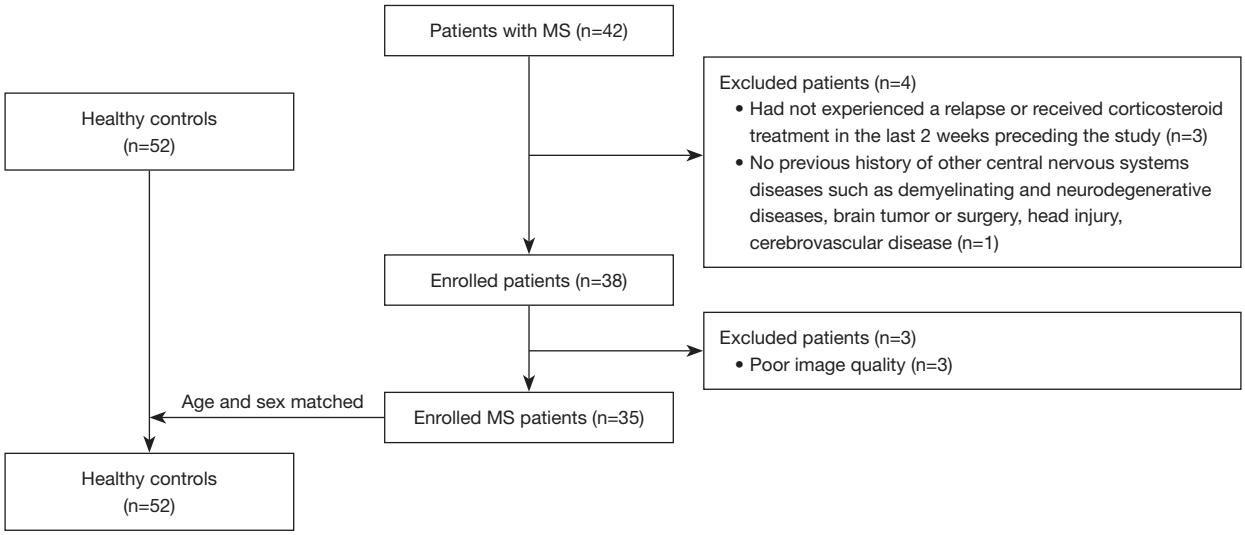

Figure 1 Screening process for the included MS patients and healthy controls. MS, multiple sclerosis.

repetition time (TR) =5,669 ms, echo-train length (ETL) =16, number of excitation (NEX) =2, bandwidth =31.25 kHz, phase acceleration factor =2.5, slice thickness/gap =3/0.6 mm, 38 slices for whole brain coverage, total scan time is 7 min 30 s.

High-resolution images were acquired with a three-dimensional brain volume (3D-BRAVO) sequence: matrix =240×240, FOV =240 mm × 240 mm, TR =6.0 ms, TE =2.9 ms, prep time =400, flip angle =12°, bandwidth =35.71 kHz, NEX =2, phase acceleration factor =2, slice thickness/gap =1/0 mm, slice number =176. The scan time for 3D-BRAVO was 3 min 34 s.

Image processing and analysis

Relaxation maps generated from the MAGiC images were selected for quantitative analysis using SyMRI 8.0 software (SyntheticMR AB, Linköping, Sweden). The total volume includes intracranial volume (ICV), brain parenchymal volume (BPV), myelin volume (MYV), cerebral spinal fluid volume (CSFV), white matter volume (WMV), gray matter volume (GMV), myelin fraction (MYF = MYV/BPV), and brain parenchymal fraction (BPF = BPV/ICV) were also acquired by automatic brain segmentation. The T1, T2, and PD maps provide an absolute scale and hence a robust input to brain segmentation for WM, GM, and CSF. The ICV corresponds to the sum of BPV and CSF. BPV was calculated as the sum of WM, GM, and non-WM/GM/CSF. MYV contains the myelin water and myelin sheaths. The short-time component of the observed T2 relaxation represents the presence of water trapped between the myelin sheaths, termed myelin water. MYV can be automatically calculated in the latest version of the SyMRI software.

Global volumetry and relaxometry data were processed using the following steps: Firstly, rigid registration between the 3D-BRAVO images and the relaxation maps was conducted using SPM12 (www.fil.ion.ucl.ac.uk/spm/software/spm12). Secondly, the individual images of tissue probability maps and normalized relaxation maps were obtained from native space to standard Montreal Neurological Institute (MNI) templates (http://www.mni.mcgill.ca/) via segmentation and normalization using the CAT12 toolbox (http://www.neuro.unijena.de/cat/). The global relaxometry in GM was calculated by averaging the relaxation values from voxels with GM partial volume exceeding 95%. Finally, the brain regional GM volumetry and relaxometry in 33 selected regions were extracted according to the anatomical automatic labeling (AAL) template (22). The post-processing pipeline as shown in *Figure 2*.

Statistical analysis

All statistical analyses were performed using MATLAB R2020a and SPSS version 22.0 software (SPSS, Chicago, IL, USA). Normal distribution assumption was checked utilizing Kolmogorov-Smirnov and Shapiro-Wilk tests.

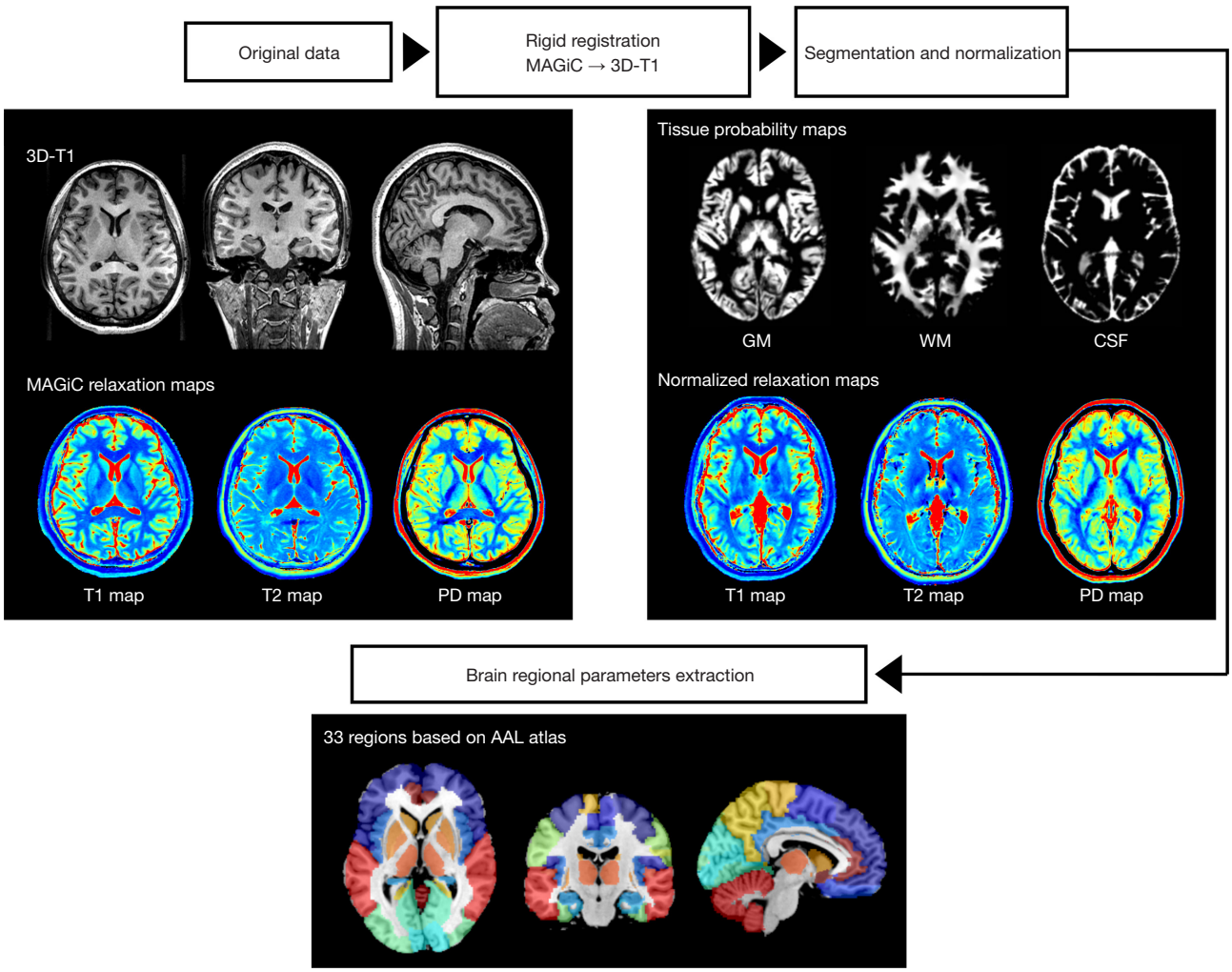

Figure 2 The post-processing pipeline using synthetic MRI (MAGiC) examination. MRI, magnetic resonance imaging; MAGiC, MAGnetic resonance image Compilation; GM, gray matter; WM, white matter; CSF, cerebral spinal fluid; PD, proton density; AAL, anatomical automatic labeling.

Student *t*-tests were used to compare demographic and clinical data (age, education, and ICV) conforming to normal distribution. Chi-square tests were used to examine gender between two groups.

The global brain volumetry, regional brain T1, T2, and PD values between MS patients and HCs were compared using analysis of covariance (ANCOVA). Correlational analyses were performed to determine the correlations of quantitative parameters and clinical variables (EDSS scores, illness duration) using MS patients. The ICV, gender, education, and age were considered as covariates for the following ANCOVA and correlational analyses. Multiple comparisons of all brain regional analyses were controlled by Bonferroni correction according to 33 selected brain regions. A corrected $P<0.05$ was considered statistically significant. The significant brain subregions were shown by MRIcron software.

Results

Initially, 42 patients were recruited, with 7 subsequently excluded. In the final study cohort, 35 MS patients and 52 age-matched HCs were included. No significant differences in age (P=0.0864) and gender (P=0.5018) were found between the MS patients compared with HCs groups. The illness duration of MS patients ranged from 0.5 to

Table 1 Demographics and clinical data of participants

Variables	MS (n=35)	HC (n=52)	χ^2/t	P
Gender (male/female)	11/24	20/32	χ^2=0.4517	0.5018
Age (years), mean ± SD	32.94±10.073	29.31±9.243	t=1.7349	0.0864
Illness duration (months), median (IQR; range)	36 (12–68; 0.5–240)	NA		
Education (years)	13.66±2.300	14.29±2.269	t=1.265	0.209
EDSS score, mean ± SD	3.014±1.358	NA		
ICV	1,378.143±119.443	1,453.731±121.389	t=2.866	0.0052

MS, multiple sclerosis; HC, healthy control; IQR, interquartile range; EDSS, Expanded Disability Status Scale; ICV, intracranial volume.

Table 2 Comparison of global volumetry and relaxation values between MS patients and HC group

Variables	HC	MS	t	P
Global volumetry				
GMV (mL)	626.175±89.486	613.120±65.388	1.7459	0.1904
WMV (mL)	579.903±68.432	472.249±58.505	43.9486	<0.001***
CSFV (mL)	177.017±39.729	241.294±81.805	–38.7301	<0.001***
MYV (mL)	192.457±27.381	151.883±22.766	38.1444	<0.001***
BPV (mL)	1,276.712±107.368	1,136.771±106.126	38.8223	<0.001***
MYF (MYV/BPV)	13.231±1.465	11.034±1.529	6.7395	<0.001***
BPF (BPV/ICV)	87.85±2.392	82.623±5.368	5.4115	<0.001***
Global GM relaxometry				
T1	1321.565±73.652	1420.485±49.207	–43.7581	<0.001***
T2	103.014±4.474	113.877±10.819	–39.6669	<0.001***
PD	67.55±2.507	83.082±0.878	–10.9375	0.0013**

**, P<0.01; ***, P<0.001. MS, multiple sclerosis; HC, healthy control; GMV, gray matter volume; WMV, white matter volume; CSFV, cerebral spinal fluid volume; MYV, myelin volume; BPV, brain parenchymal volume; MYF, myelin fraction; BPF, brain parenchymal fraction; ICV, intracranial volume; GM, gray matter; PD, proton density.

250 months, with a median duration of 48 months. The mean EDSS score was 3.014±1.358 (see *Table 1*).

Quantification of global volumetry

Results of global volumetry differences between the MS patients and HCs are shown in *Table 2*. The global volumetry including WMV, MYV, and BPV were all significantly lower than MS patients, as well as a higher CSFV (P<0.001). Similarly, BPF and MYF were significantly lower in MS patients (all P<0.01).

There was no statistical difference in global GMV between the two groups (P>0.05). For regional GM volume measurements, several regions in the MS patients were significantly demonstrated smaller than those of HCs (P<0.05, corrected) (see Table S1, *Figure 3*).

Quantification of global relaxometry

For global GM relaxometry, the T1, T2, and PD values were higher in MS patients than those in HCs, respectively (P<0.05) (see *Table 2*).

For regional GM relaxometry, the T1, T2, and PD values of several regions showed significant differences between MS patients and HCs (P<0.05, corrected) (see Table S2, *Figure 4*, Figure S1A-S1C).

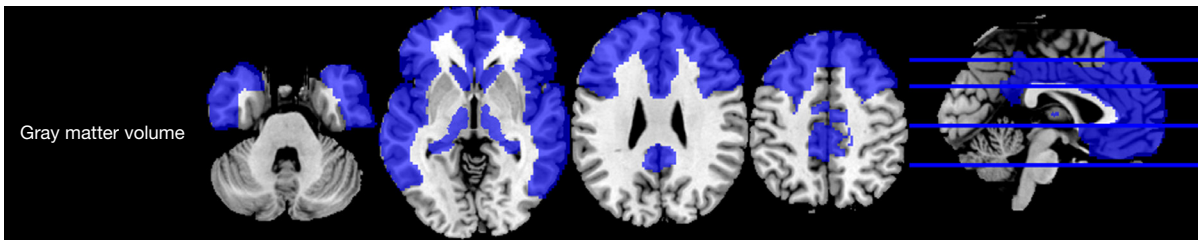

Figure 3 For regional GM volume measurements, a number of regions in the MS patients were significantly demonstrated smaller than those of HCs (P<0.05, corrected). The significant brain subregions overlaid on top of a standard brain were shown by MRIcron software. GM, gray matter; MS, multiple sclerosis; HC, healthy control.

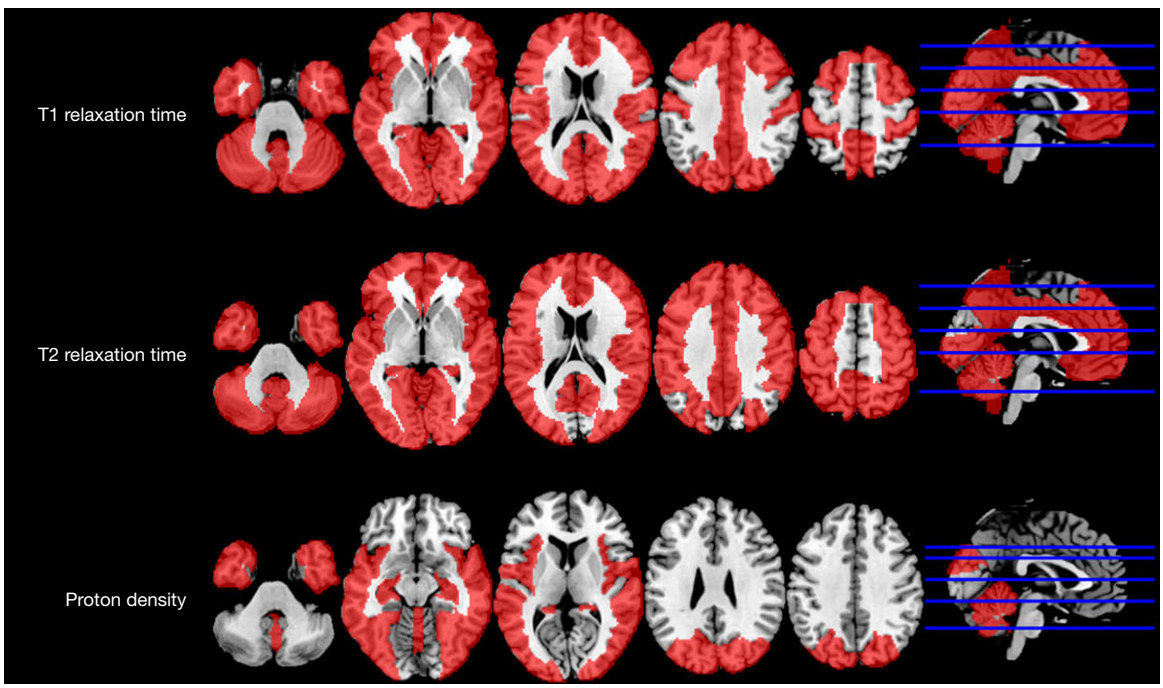

Figure 4 For regional GM relaxometry, the T1, T2 and PD values of several regions showed significantly differences between MS patients and HCs (P<0.05, corrected). The significant brain subregions overlaid on top of a standard brain were shown by MRIcron software. GM, gray matter; MS, multiple sclerosis; PD, proton density; HC, healthy control.

Correlations between quantitative parameters and clinical variables

The global GMV and BPV have shown in *Table 3* decreased as the EDSS scores increased (P<0.05). Furthermore, a significant negative correlation was found between regional GM volumetry (olfactory and rectus) and EDSS scores (P<0.05, corrected). But there were no significant correlations between illness duration and quantitative parameters (P>0.05, corrected).

Discussion

Volumetric characteristics

Brain atrophy is considered an important prognostic factor in the assessment of subsequent disability (23-25). Our findings indicated that brain atrophy in MS patients may involve the entire brain, including myelin and WM, suggesting that the pathophysiology of MS patients may be related to the whole brain not only limited to some specific

Table 3 Correlations between the quantitative parameters and clinical variables (n=35) (only parameters that showed significant correlations are shown in the table)

Variables	EDSS	
	r	Significance
Global volumetry		
GMV	−0.353	0.038
BPV	−0.357	0.035
Regional GM volumetry		
Olfactory	−0.383	0.023
Rectus	−0.356	0.036

EDSS, Expanded Disability Status Scale; GMV, gray matter volume; BPV, brain parenchymal volume; GM, gray matter.

brain regions. The potential neuropathology leads to brain atrophy, and synthetic MRI can monitor these volumetric variations.

The pathology of GM lesions differs from that of WM lesions (26). Some extent axonal transaction can be found in cortical GM lesions in addition to the glial, synaptic, and neuronal deficits (26), which may be necessary for illustrating the consistent findings of cortical thinning and GM atrophy in MS measured by MRI (27).

Different MRI-based techniques (automatic, semi-automatic, and manual) have been applied to measure global and regional brain atrophy. In the current, we have investigated the utility of synthetic MR imaging to determine the atrophic brain regions in MS. Reduced global brain volumetry and increased CSF volume indicated brain atrophy. Significantly lower BPF in patients with MS has been demonstrated by synthetic MRI volumetry. Meanwhile, a reduction of MYV was still found in MS patients, indicating that myelin content decreased. The results are consistent with previous findings (using other methodologies) (24,25,28).

Though we did not find significant global GM atrophy in our present research, which is inconsistent with previous studies (29), multiple significant GM atrophic regions were still detected in MS patients. GM atrophy, which contributes to the multiple atrophic brain regions in patients suffering from MS, may reflect a combination of neurite transaction (30), demyelination, and reduced synapse or glial densities (31,32). Our findings confirm that GM atrophy is not uniform across the brain in MS, and some regions are more vulnerable to atrophy than others (33). These findings are consistent with other histopathological or MR studies, which showed atrophy and demyelinated lesions in GM structures such as the amygdala, pallidum, caudate, thalamus, hypothalamus, hippocampus, and putamen (14,26,34,35). Of course, another possible reason may be the insufficient samples. A larger-sample study should be performed to further investigate the global GM atrophy in the MS.

Relaxometry characteristics

Normal brain tissues have a relatively narrow range of T1, T2, and PD values, while pathological tissues exhibit distinctly deviated values (36). Neuronal and axonal loss or death, water content changes, and demyelination can cause changes in relaxation times even if the tissues appear normal on imaging (37,38). This may speculate about the underlying pathophysiology of MS and have clinical implications in predicting disease progression in MS (i.e., possible resultant neuronal damage and demyelination). Relaxometry is sensitive to the microstructure and composition of the brain and can potentially reveal the alterations of specific brain tissue (13).

We found significantly high T1 values in the selected GM regions in MS patients. These results are similar to the previous studies that showed a prolonged T1 (39,40). Although changes in T1 relaxation time may be related to myelin loss, iron load, amyloid burden, and water content in MS patients, inconsistent results of T1 alterations in GM have been reported (41,42). Previous studies have revealed that hyperintensity of T1-weighted in lesions attributed to T1 shortening, possibly due to remyelination or macrophage activity (13). Thus, the influence of MS on T1 values may be complex (13).

Previous studies have shown that T2 relaxation time was associated with amyloid deposits, myelin density, iron load, and tissue water content (43,44). Our results showed significantly higher T2 values in MS compared to HCs, which is consistent with previous studies. The prolongation of T2 may be due to gliosis, axonal and myelin loss, and increased water content. However, it is difficult to identify which factor plays a dominant role in the changes to T2 value.

PD values can reflect the tissue water content and thus infer the structural damage to the brain. However, there were relatively few studies of PD values in patients with MS. In our work, fewer GM brain regions had PD higher value in MS patients than in normal controls. The reason

for this may be because PD is generally less sensitive to pathophysiology than T1 and T2. Future studies are still needed.

Interestingly, there were no significant microstructure alterations common to the MS patients in the deep GM nuclei (caudate, putamen, pallidum), while the atrophy of deep GM nuclei existed. The pathological process of patients with MS is complex. We can speculate that atrophy in the cortical GM in patients with MS is relatively more sensitive and extensive.

Correlations between quantitative parameters and clinical variables

Moreover, there was a strong correlation between global volumetry (GMV and BPV) and EDSS scores. Previous studies have demonstrated the strongest correlations in the advanced stages of MS, and cortical atrophy occurs even before clinical symptoms become apparent (45). Another report has also confirmed that a higher EDSS score was correlated with a higher degree of atrophy (25,39).

We found a statistically significant negative correlation in two out of 33 selected GM regions in MS patients. There were no correlations in other regions. None of the measured GM volumetric or relaxometric metrics showed any association with the illness duration. There are two possible reasons: first, the pathophysiological alterations in brain GM may be global during pathology rather than restricted to a single region. Second, the relatively small sample size may have limited the significance of altered regional GM relaxometry, especially when the number of brain regions to be analyzed was relatively large.

The present study still has some limitations. (I) This study was limited to exploring MS disease and normal controls and did not provide an in-depth comparative analysis of subtypes. Future studies should focus on the characteristics of subtypes of MS. (II) We did not analyze the focal MS plaques characteristics in the present study. The plaque characteristics should also be further explored in the future. (III) We did not evaluate the cognitive function in MS patients. More studies will be explored the association between cognitive function and image characteristics.

Conclusions

These findings suggest that MS patients had global and regional brain volumetry and relaxometry alterations, and the synthetic MRI-derived parameters may be potentially used as specific quantitative markers for the clinic to improve the understanding of MS.

Acknowledgments

The authors thank Dr. Yongnan Mu (Department of Medicine, Englewood Hospital, Englewood, NJ, USA) for polishing the language, and Lizhi Xie from GE healthcare for expert technical assistance with MRI.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-21-970/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-21-970/coif). PW reports that he is the employee of GE Healthcare, which developed the data post-processing method used in this paper. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Research Ethics Committee of China Medical University, and informed consent was provided by all participants.

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Cite this article as: Cao J, Xu X, Zhu J, Wu P, Pang H, Fan G, Cui L. Rapid quantification of global brain volumetry and relaxometry in patients with multiple sclerosis using synthetic magnetic resonance imaging. Quant Imaging Med Surg 2022;12(6):3104-3114. doi: 10.21037/qims-21-970

Supplementary

Table S1 Comparison of regional GM volumetry between multiple sclerosis (MS) patients and healthy controls (HC)

Regional GM volumetry	HC	MS	T	P (Bonferroni-corrected)
Precentral	16.128±4.315	13.661±3.842	1.5399	1.0000
Frontal	102.563±12.226	89.211±10.118	3.3770	0.0365*
Rolandic	8.169±1.110	6.927±1.144	3.1769	0.0685
Supp_Motor	12.513±2.152	10.453±1.863	2.9862	0.1218
Olfactory	2.770±0.397	2.311±0.344	3.6996	0.0126*
Rectus	6.624±0.704	5.661±0.693	4.6053	0.0005***
OFC	13.562±1.538	12.326±1.293	1.8576	1.0000
Insula	16.086±1.570	13.940±1.779	3.9722	0.0049**
Cingulate	17.136±2.149	13.887±2.416	4.6432	0.0004***
Hippocampus	8.032±0.857	6.866±1.030	4.0618	0.0036**
ParaHippocampal	6.941±1.268	6.276±0.918	1.0951	1.0000
Amygdala	2.038±0.453	1.833±0.376	1.4841	1.0000
Calcarine	10.680±2.612	9.050±2.105	1.7171	1.0000
Cuneus	7.682±1.456	6.664±1.422	1.8428	1.0000
Lingual	12.512±2.421	11.369±1.757	0.9659	1.0000
Occipital	27.835±5.016	24.339±4.706	1.7920	1.0000
Fusiform	19.863±2.631	17.220±2.139	3.0624	0.0970
Postcentral	18.204±4.144	15.543±3.646	1.6709	1.0000
Parietal	21.203±4.709	18.654±3.960	1.5235	1.0000
SupraMarginal	9.567±1.709	7.981±1.806	2.5687	0.3945
Angular	9.525±1.541	8.364±1.531	1.9806	1.0000
Precuneus	19.967±3.182	17.284±2.801	2.3493	0.6973
Paracentral_Lobule	4.874±1.247	3.998±1.000	2.2413	0.9113
Caudate	4.797±1.154	3.110±1.463	4.2038	0.0021**
Putamen	7.215±2.448	5.841±1.699	2.0535	1.0000
Pallidum	0.840±0.229	0.790±0.264	0.6333	1.0000
Thalamus	6.779±2.180	4.231±1.978	4.1212	0.0029**
Heschl	1.605±0.282	1.306±0.270	3.2832	0.0492*
Temporal	88.490±11.810	74.900±10.553	3.6469	0.0151*
Cerebelum	67.128±13.097	62.026±10.191	1.0235	1.0000
Vermis	5.403±0.895	4.783±0.984	2.0430	1.0000
ACC	9.436±1.176	7.946±0.908	4.5909	0.0005***
NAC	1.409±0.249	0.988±0.322	5.1787	0.0000***

*, P<0.05; **, P<0.01; ***, P<0.001.

https://dx.doi.org/10.21037/qims-21-970

Table S2 Comparison of regional GM relaxometry between multiple sclerosis (MS) patients and healthy controls (HC)

Brain region	T1				T2				PD			
	HC	MS	T	P	HC	MS	T	P	HC	MS	T	P
Precentral	1411.655±162.223	1536.238±195.443	−3.0633	0.0967	117.091±14.936	143.195±44.066	−3.5297	0.0223	82.063±2.870	82.876±2.773	−1.5234	1.0000
Frontal	1424.104±65.595	1519.273±77.484	−5.3246	0.0000***	116.495±8.842	130.693±17.302	−4.6166	0.0005***	83.550±1.659	83.927±1.338	−1.4110	1.0000
Rolandic	1328.826±140.706	1507.805±124.322	−5.2122	0.0000***	108.439±11.839	132.999±22.074	−5.9566	0.0000***	79.770±3.185	82.257±1.763	−3.7579	0.0103*
Supp_Motor	1422.831±94.587	1503.147±131.365	−3.2571	0.0534	120.091±15.646	133.570±26.674	−2.8802	0.1659	81.894±2.963	82.072±3.243	−0.5165	1.0000
Olfactory	1268.269±87.037	1354.272±62.428	−4.4505	0.0009***	101.456±7.634	110.817±8.890	−4.6928	0.0003***	82.860±1.820	82.325±1.364	1.3012	1.0000
Rectus	1304.687±73.312	1420.138±101.597	−5.4460	0.0000***	98.353±4.806	106.691±8.070	−5.2937	0.0000***	83.713±2.018	84.036±1.677	−1.0601	1.0000
OFC	1386.150±133.326	1468.596±81.730	−3.2772	0.0501	102.453±5.343	108.808±6.153	−4.9923	0.0001***	83.444±3.163	84.659±2.113	−2.8641	0.1738
Insula	1322.590±102.269	1454.614±72.524	−6.2098	0.0000***	107.458±6.769	125.683±15.463	−7.0713	0.0000***	80.913±2.580	82.545±0.824	−3.5242	0.0227*
Cingulate	1314.415±94.945	1446.856±87.550	−5.6758	0.0000***	96.364±4.549	106.851±11.783	−5.0748	0.0001***	82.610±2.279	83.427±0.806	−1.7023	1.0000
Hippocampus	1257.193±103.403	1393.245±107.632	−5.1608	0.0001***	102.471±6.379	122.668±22.082	−5.4240	0.0000***	81.631±2.827	84.066±1.527	−3.7733	0.0098**
ParaHippocampal	1331.919±76.794	1403.944±82.553	−4.0526	0.0037**	103.567±7.294	113.233±13.66	−4.1980	0.0022**	83.194±1.869	84.006±1.136	−2.1684	1.0000
Amygdala	1175.373±76.369	1253.377±80.384	−4.5857	0.0005***	92.683±3.660	101.713±8.950	−6.1113	0.0000***	80.765±2.054	81.355±1.238	−1.5104	1.0000
Calcarine	1232.061±123.880	1399.298±130.842	−4.8494	0.0002***	97.145±10.048	113.047±19.467	−4.0230	0.0041**	77.668±2.943	79.868±2.311	−3.2429	0.0558
Cuneus	1283.989±125.185	1465.207±187.758	−4.2182	0.0020**	95.381±7.936	113.888±33.080	−2.9276	0.1446	79.364±2.109	81.267±1.873	−3.5962	0.0179*
Lingual	1165.043±77.825	1287.562±68.574	−6.1729	0.0000***	86.663±3.181	94.344±6.338	−5.9314	0.0000***	78.095±2.233	79.578±0.996	−3.0974	0.0873
Occipital	1235.124±86.244	1329.778±84.413	−4.2580	0.0017**	91.978±4.909	98.654±10.998	−3.3558	0.0391*	80.979±1.845	83.002±2.214	−4.5644	0.0006***
Fusiform	1241.730±74.165	1348.623±67.124	−6.1864	0.0000***	91.716±2.880	100.003±8.577	−5.6106	0.0000***	81.831±1.917	83.322±0.821	−4.1074	0.0030**
Postcentral	1526.828±170.774	1663.012±153.953	−3.3628	0.0382*	136.446±26.934	169.617±50.478	−3.7402	0.0110*	82.631±2.526	83.436±1.561	−1.5343	1.0000
Parietal	1437.522±142.766	1546.329±141.643	−3.1674	0.0705	118.741±18.553	141.829±33.350	−3.9696	0.0050**	82.553±1.779	82.749±1.351	−0.7719	1.0000
SupraMarginal	1387.245±184.821	1493.729±156.696	−2.5383	0.4277	111.936±17.482	131.434±32.760	−3.4158	0.0323*	80.168±2.635	81.586±2.746	−2.9374	0.1405
Angular	1317.795±115.456	1405.753±112.106	−2.9504	0.1353	98.568±7.453	106.783±15.377	−3.1453	0.0754	82.755±1.939	83.755±2.014	−2.3219	0.7468
Precuneus	1316.013±99.369	1444.809±116.541	−4.6535	0.0004***	101.271±9.051	116.841±25.194	−3.4861	0.0257*	81.013±1.802	82.173±0.918	−2.8377	0.1875
Paracentral_Lobule	1444.213±162.843	1590.526±296.095	−2.7857	0.2173	116.513±15.904	144.838±60.710	−2.9100	0.1522	82.226±2.878	82.539±4.312	−0.6023	1.0000
Caudate	1241.583±113.921	1294.622±165.944	−1.1942	1.0000	100.161±18.549	109.316±25.882	−1.3399	1.0000	81.807±1.877	81.320±2.030	0.9856	1.0000
Putamen	969.412±79.372	994.481±33.751	−1.7302	1.0000	72.023±2.982	71.782±2.896	−0.6683	1.0000	77.016±2.770	77.531±1.850	−0.9038	1.0000
Pallidum	965.500±66.709	953.775±72.075	0.2631	1.0000	69.088±4.413	67.170±5.316	0.8712	1.0000	76.498±2.359	75.466±3.370	1.1901	1.0000
Thalamus	1013.351±126.173	1182.432±294.583	−3.1868	0.0664	82.952±10.051	106.221±46.782	−2.9824	0.1231	75.726±2.454	76.771±3.738	−1.2156	1.0000
Heschl	1403.241±199.762	1599.822±229.666	−3.6106	0.0170*	114.456±30.031	146.295±51.174	−2.8972	0.1580	80.600±2.758	82.567±2.660	−2.9466	0.1368
Temporal	1362.011±71.507	1459.109±60.272	−5.4545	0.0000***	102.713±4.956	112.793±11.776	−4.7053	0.0003***	82.632±1.921	84.041±1.042	−4.3477	0.0013**
Cerebelum	1267.722±134.560	1395.009±70.884	−4.1435	0.0027**	93.058±7.710	100.943±5.941	−4.0252	0.0041**	81.041±6.895	84.851±1.605	−1.9907	1.0000
Vermis	1394.479±91.143	1494.077±133.648	−4.2572	0.0018**	111.248±10.196	121.496±17.142	−3.2957	0.0473*	83.853±1.465	85.029±1.389	−3.5463	0.0211*
ACC	1350.055±87.546	1454.549±82.395	−4.9471	0.0001***	104.669±6.168	115.303±12.923	−4.8192	0.0002***	82.814±1.915	83.515±0.882	−1.6264	1.0000
NAC	1130.935±74.210	1173.442±48.857	−2.7704	0.2268	87.800±6.254	89.645±6.781	−1.3672	1.0000	81.527±1.471	81.582±1.010	−0.1115	1.0000

*, P<0.05; **, P<0.01; ***, P<0.001.

https://dx.doi.org/10.21037/qims-21-970

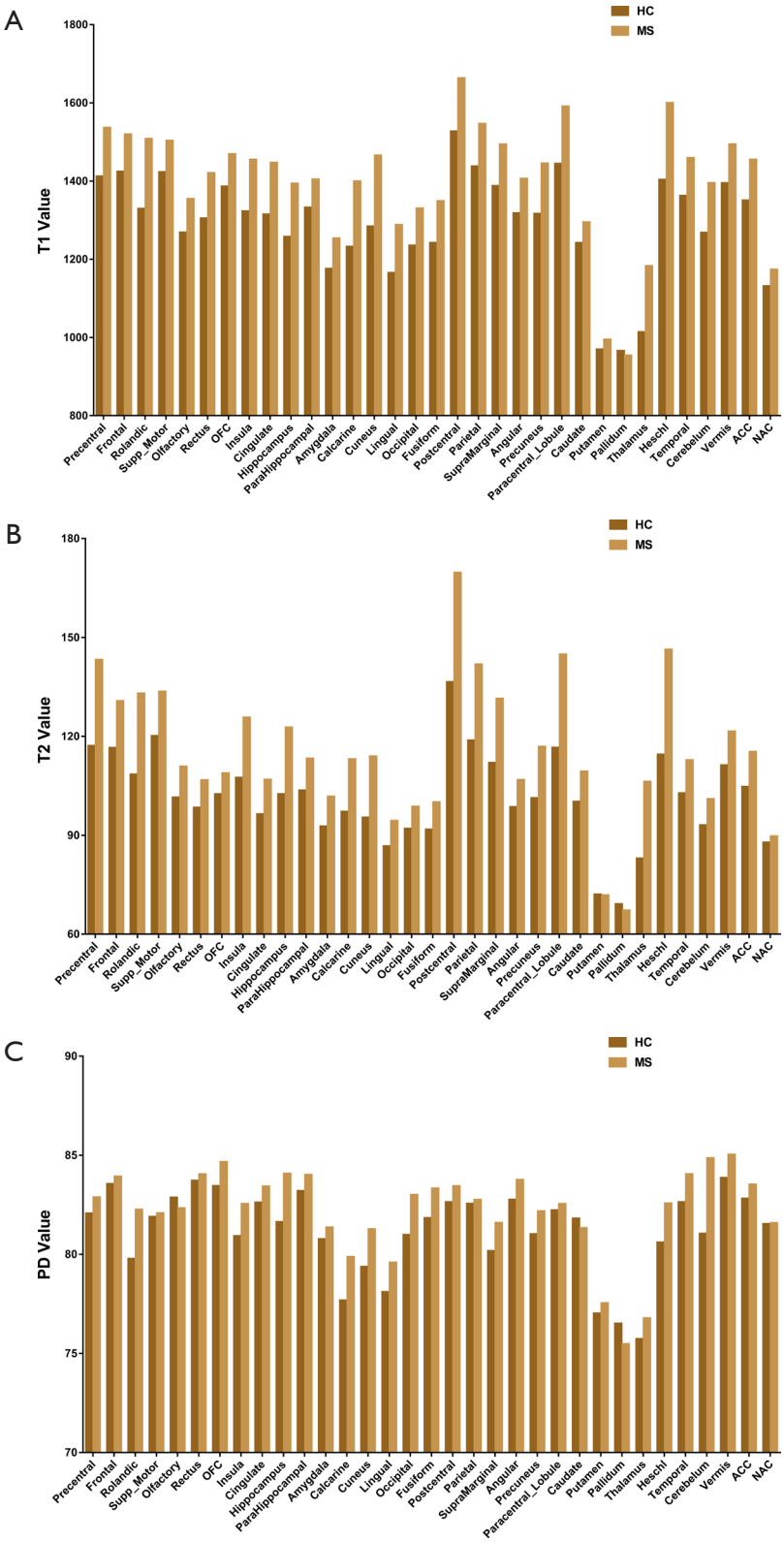

Figure S1 Regional GM relaxometry, the T1 (S1A), T2 (S1B) and PD values (S1C) of several regions showed significantly differences between MS patients and HCs (P < 0.05, corrected).

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