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Clinical Feasibility of Automated Brain Tissue and Myelin Volumetry of Normal Brian Using Synthetic Magnetic Resonance Imaging With Fast Imaging Protocol: A Single-Center Pilot Study

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Objective: This study aimed to investigate the clinical feasibility of synthetic magnetic resonance imaging (MRI) with fast imaging protocol for automated brain tissue and myelin volumetry in healthy volunteers at 3.0-T MRI.

Methods: Thirty-four healthy volunteers were scanned using synthetic MRI with 3 sets of scan parameters: groups Fast (FAS; 2 minutes, 29 seconds), Routine (ROU; 4 minutes, 7 seconds), and Research (RES; 7 minutes, 46 seconds). White matter (WM), gray matter (GM), cerebrospinal fluid (CSF), non-WM/GM/CSF (NoN), brain parenchymal volume (BPV), intracranial volume (ICV), and myelin volume (MYV) were compared between 3 groups. Linear correlation analysis was performed for measured volumes of groups FAS and ROU versus group RES.

Results: Significant differences were found in all the measured brain tissue volumes between groups FAS and ROU ($P < 0.001$), FAS and RES ($P < 0.05$), and ROU and RES ($P < 0.05$), except for NoN between groups ROU and RES ($P = 0.0673$), ICV between groups FAS and ROU ($P = 0.2552$), and ICV between groups FAS and RES ($P = 0.4898$). The intergroup coefficients of variation were 4.36% for WM, 6.39% for GM, 10.14% for CSF, 67.5% for NoN, 1.21% for BPV, 0.08% for ICV, and 5.88% for MYV. Strong linear correlation was demonstrated for WM, GM, CSF, BPV, ICV, and MYV ($R = 0.9230$–1.131) between FAS versus RES, and ROU versus RES.

Conclusions: Using synthetic MRI with fast imaging protocol can change the measured brain tissue volumes of volunteers. It is necessary to use consistent acquisition protocols for comparing or following up cases quantitatively.

Key Words: synthetic MRI, quantitative MRI, fast scan, brain tissue volume, segmentation

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Segmentation and volume estimation of brain tissues, such as gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF), are important in evaluating neurological disorders,[1,2] such as WM hyperintensity,[3] multiple sclerosis,[4] traumatic brain injury,[5] Alzheimer disease,[6] and other forms of dementia.[7] Quantitative brain volume segmentation can also be helpful in providing additional objective data on treatment evaluation and longitudinal follow-up of disease progression.[8] Currently, the most commonly used brain segmentation methods rely on the signal intensity, which is based on the conventional contrast-weighted magnetic resonance (MR) images, and related offline methods such as statistical parametric mapping (SPM), FreeSurfer, et al.[9] However, these methods involve complex postprocessing steps and are relatively time-consuming. Furthermore, acquisition parameters and scanner settings can potentially influence the signal intensities of conventional contrast-weighted images. These drawbacks limit their wide use in routine clinical practice.

Synthetic magnetic resonance imaging (MRI), which uses multidynamic multiecho sequence, enables acquisition of quantitative T1, T2, and proton density (PD) values of the whole brain within approximately 6 minutes.[10] Combinations of T1, T2, and PD values can be used to segment brain tissues such as intracranial volume (ICV), GM, WM, and CSF by using a commercial software (SyntheticMR AB, Linköping, Sweden), and the postprocessing time is less than 1 minute.[10,11] Myelin volume fraction (MYF) can also be calculated based on a model where each acquisition voxel is composed of 4 partial volumes (myelin, cellular, free water, and excess parenchymal water) and has its own R1, R2, and PD values.[12] The promising results are shown in the imaging of central nervous system diseases, such as multiple sclerosis[13,14] and neurodegenerative diseases.[15] Previous studies also showed that GM and WM estimation agree well with SPM analyses,[16] and the repeat measurement errors for brain parenchymal volume (BPV), ICV, brain parenchymal fraction, and GM fraction measured by synthetic MRI were significantly lower than those measured by FreeSurfer, FSL, or SPM at 3.0-T MRI scanner.[13]

However, in clinical practice, multidynamic multiecho sequences with fast imaging protocols need to be applied for motion-prone patients, such as pediatric patients and recent stroke patients. Because the quantitative parameters represent physical constants that are presumably intrinsic to a given tissue or other material, changing image acquisition parameters theoretically should not alter them; however, model-based derivations of these parameters from real data cannot be expected to be perfectly reproducible. Previous studies showed that brain tissue and myelin volumetry derived from synthetic MRI were robust with different in-plane resolutions in 1.5 T,[17] but differences were found in some brain regions in 3.0-T MRI scanner.[12] To the best of our knowledge, there are very limited reports about fast imaging parameter-dependent changes of brain tissue segmentation and volume estimation using synthetic MRI.

Hence, the aim of this study was to investigate the clinical feasibility of synthetic MRI with fast imaging protocol (less than

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TABLE 1. Scan Parameters of 3 MDME Sequences

	TE1, ms	TE2, ms	TR, ms	ETL	Matrix	Bandwidth, kHz	AF	Pixel Size, mm	Scanning Time
FAS	18.8	94.1	4137	16	288 × 224	25	3.0	0.8 × 1.1	2 min, 29 s
ROU	21.8	87.1	4000	12	320 × 256	22.73	2.5	0.8 × 0.9	4 min, 07 s
RES	26.1	104.6	4316	12	384 × 288	20.83	1.5	0.6 × 0.8	7 min, 46 s

TE indicates echo time; TR, repetition time; ETL, echo train length; AF, acceleration factor.

3 minutes) for brain tissue volumetry in healthy individuals on 3.0-T MRI scanner.

MATERIALS AND METHODS

Subjects

This study was approved by our institutional review board, and informed consent were written by all the participants. Thirty-four healthy volunteers (13 men, 21 women; mean age, 39.2 years; age range, 22–61 years) were included. None of the participants had a history of a major medical condition, or neurological or psychiatric disorder, and no abnormalities were found on brain MRI.

MRI Acquisition

All MRI examinations were performed on a 3.0-T MRI scanner (SIGNA Pioneer; GE Healthcare, Milwaukee, WI) using a 32-channel head coil. Quantitative MRI was performed using MAGiC sequence (Magnetic Resonance Image Compilation). This sequence is a multisection, multiecho, multisaturation delay method of saturation recovery acquisition that uses a fast spin-echo readout.[10] A single basic block of this quantification sequence consists of 2 phases. In the first saturation phase, a slice-selective saturation pulse with flip angle θ is performed on slice n, followed by subsequent spoiling the signal ("saturation"). In the second acquisition phase, a slice-selective fast spin-echo acquisition is performed on another slice m ("acquisition"), consisting of multiple echoes, which are acquired to measure transverse relaxation time (T2). By shifting between slices m and n, a desired delay time can be set between the saturation and acquisition of each specific slice. The longitudinal relaxation time (T1) after a saturation pulse can be retrieved from multiple scans, by using different delay times. Because the number of scans and delay times can be freely chosen, the dynamic range of T1 can also be set as desired.[10] Two echo times and 4 delay times were used to quantify longitudinal T1 and transverse T2 relaxation times, and 8 complex images per slice were produced. To retrieve T1, T2, and PD maps, while accounting for B1 inhomogeneity, a least square fit was performed on the signal intensity (I) of images by minimizing the following equation:

$$I = A \cdot \mathrm{PD} \cdot \exp(-\mathrm{TE}/\mathrm{T2}) \times \frac{1 - \{1 - \cos(B_1\theta)\}\exp(-\mathrm{TI}/\mathrm{T1}) - \cos(B_1\theta)\exp(-\mathrm{TR}/\mathrm{T1})}{1 - \cos(B_1\alpha)\cos(B_1\theta)\exp(-\mathrm{TR}/\mathrm{T1})}$$

where α is the applied excitation flip angle (90°) and θ is the saturation flip angle (120°). A is an overall intensity scaling factor that takes into account several elements, including sensitivity of the coil, amplification of the radiofrequency chain, and voxel volume.[11]

Multidynamic multiecho sequences with 3 sets of different scan parameters (Fast [FAS], Routine [ROU], and Research [RES]) were used for quantitative MRI (Table 1). Matrix, acceleration factor, and echo train length are commonly used MRI acquisition parameters, which affect the scan time, and the 3 sets of scan parameters were set according to different combinations of these parameters. The slice thickness/gap was 4.0/1.0 mm. The field of view was 240 mm × 240 mm. The sections were 26. To achieve a relatively high image quality, we chose the permitted lowest in-plane resolution of 0.8 mm × 1.1 mm. Sequence FAS, ROU, and RES were performed on each participant.

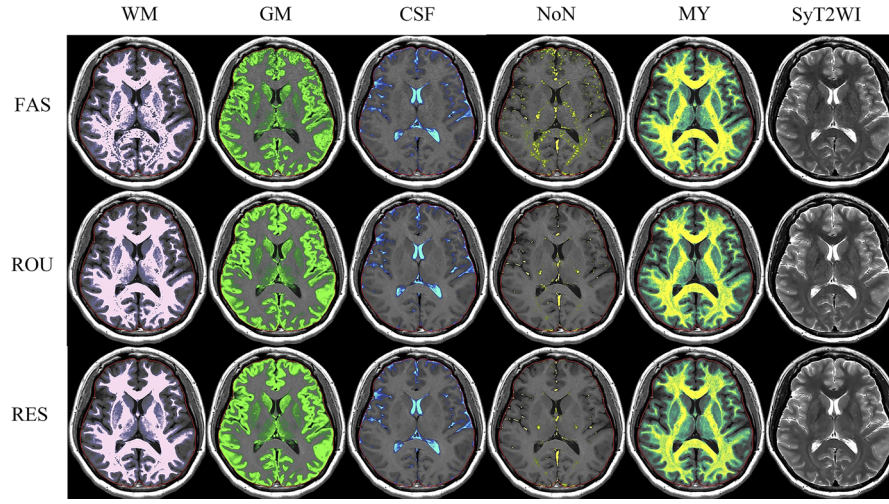

FIGURE 1. Representative images of a 26-year-old woman volunteer. White matter, GM, CSF, NoN, and MY maps are overlaid on a synthetic T1-weighted image (TR/TE = 500/10 milliseconds) in groups FAS (first row), ROU (middle row), and RES (lower row) (color overlay). Synthetic T2-weighted images of 3 groups were shown in the last column. Images can be viewed in color online at www.jcat.org. MY, myelin; SyT2WI, synthetic T2-weighted image; TE, echo time; TR, repetition time. Figure 1 can be viewed online in color at www.jcat.org.

TABLE 2. Statistical Results of Brain Tissue and Myelin Volumetry of Volunteers Among Groups FAS, ROU, and RES

	WM, mL	GM, mL	CSF, mL	NoN, mL	BPV, mL	ICV, mL	MYV, mL
FAS	572.7 ± 55.4	535.9 ± 62.4	172.3 ± 44.6	86.3 ± 22.9	1198 ± 92	1370 ± 118	208.5 ± 22.7
ROU	619.1 ± 62.9	578.4 ± 56.4	140.8 ± 40.7	28.9 ± 7.5	1227 ± 94	1368 ± 118	200.9 ± 23.8
RES	576.8 ± 60.3	609.0 ± 63.4	154.3 ± 41.7	30.3 ± 9.1	1216 ± 94	1370 ± 118	185.6 ± 21.7
P	0.013	<0.001	0.036	<0.001	0.543	0.996	0.002
Intergroup CV (%)	4.36	6.39	10.14	67.5	1.21	0.08	5.88

P values represent comparisons among 3 groups (1-way ANOVA or Kruskal-Wallis test, level of significance set at $P < 0.05$).

Image Postprocessing by Synthetic MRI

The brain tissue segmentation method by Synthetic MRI has been described in detail in previous reports.[11,18] The measured quantitative T1, T2, and PD values of brain tissues can be used as coordinates in a R1-R2-PD space. The previously reported quantitative values for WM, GM, and CSF for healthy controls derived from Synthetic MRI were used as reference values to define each brain tissue.[10] A numerical Bloch simulation was performed to investigate R1, R2, and PD for tissue mixtures and their ratios.[18] Using this method, the tissue fractions in each voxel can be calculated, and the fractions change in 0.1% increments from 0 to 100. Voxels that were not categorized as WM, GM, or CSF or mixtures of these tissues were termed non-WM/GM/CSF (NoN). The BPV was calculated as the sum of the volumes of WM, GM, and NoN. The border of the ICV was defined at a PD of 50%, assuming that the border of ICV corresponds to the interface between CSF (PD, 100%) and bone (PD, 0%),[19] and the ICV was calculated as the sum of BPV and volume of CSF.

The myelin volume (MYV) in each voxel was estimated based on a 4-compartment model (the myelin partial volume, the cellular partial volume, the free water partial volume, and the excess parenchymal water partial volume). This model postulates that the 4 compartments have their own R1, R2, and PD values and contribute to the effective R1, R2, and PD values in an acquisition voxel. The partial volume fractions of the 4 compartments were estimated by performing Bloch equations, and the MYV was calculated by multiplying the MYF by the volume of each voxel.[20] The raw Digital Imaging and Communications in Medicine data were loaded into the Synthetic MRI software (version 8.0.4; SyntheticMR AB, Linköping, Sweden), and the segmented brain tissue volumes and MYF can be obtained automatically. The total processing time for each case was less than 1 minute (Fig. 1).

Statistical Analysis

The statistical analysis was performed using GraphPad Prism 9.0. According to different sets of scan parameters, the brain volume measurements of volunteers were divided into 3 groups (groups FAS, ROU, and RES). The Kolmogorov-Smirnov test was used to assess the normality of continuous data, and all the data were normally distributed except for NoN in groups ROU and RES. Mean values and SDs for volumes of WM, GM, CSF, NoN, BPV, ICV, and MYV were extracted. Coefficients of variation (CVs) were calculated across different groups (intergroup CVs). The intergroup CV was calculated

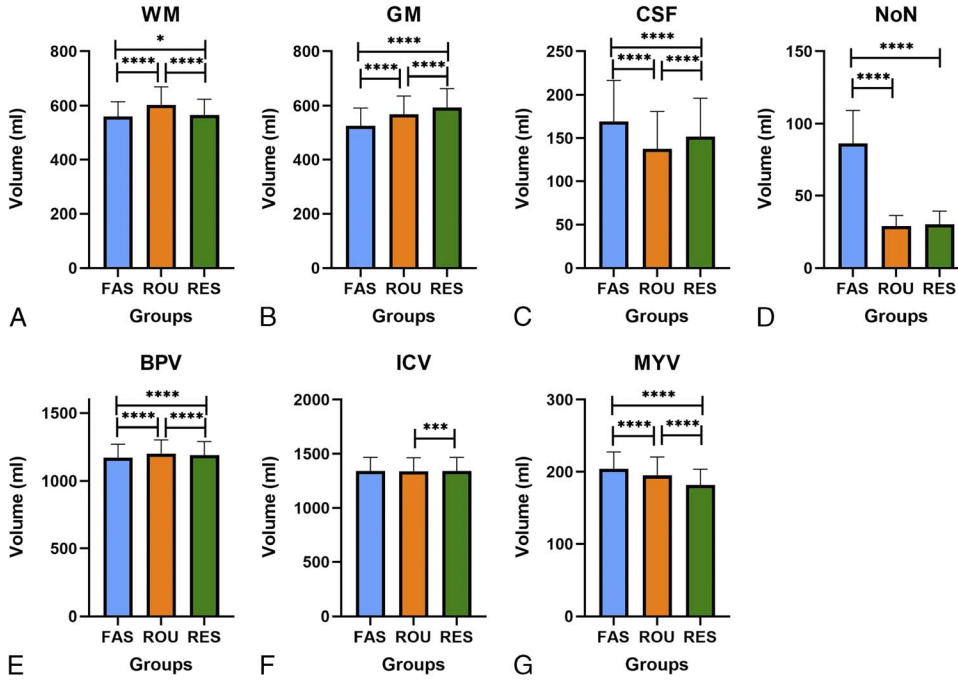

FIGURE 2. Statistical results of brain tissue and myelin volumetry of volunteers between groups FAS (blue), ROU (orange), and RES (green). Color chart, (A) to (G) (*$P < 0.05$, **$P < 0.01$, ***$P < 0.005$, ****$P < 0.001$). Figure 2 can be viewed online in color at www.jcat.org.

using the average values from each of the 3 groups. The differences of measured brain volumes between 3 groups (FAS vs RES, ROU vs RES, and FAS vs ROU) were assessed using paired-samples *t* test or Wilcoxon signed rank test (paired). Differences were considered significant at $P < 0.05$ (2-tailed).

We defined the measured brain volumes in group RES as the reference values. The linearity of brain tissue volumes between groups FAS and RES, and ROU and RES were assessed using linear regression. The bias of measured brain tissue volumes between groups FAS and RES, and groups ROU and RES were assessed using Bland-Altman plots.

RESULTS

Table 2 shows the mean volumes of WM, GM, CSF, NoN, BPV, ICV, and MYV in groups FAS, ROU, and RES. Statistically significant differences were found in all the measured brain tissue volumes between groups FAS and ROU ($P < 0.001$), FAS and RES ($P < 0.05$), and ROU and RES ($P < 0.05$), except for the NoN between groups ROU and RES ($P = 0.0673$), ICV between groups FAS and ROU ($P = 0.2552$), and ICV between groups FAS and RES ($P = 0.4898$) (Fig. 2). The intergroup CVs were 4.36% for WM, 6.39% for GM, 10.14% for CSF, 67.5% for NoN, 1.21% for BPV, 0.08% for ICV, and 5.88% for MYV.

Figure 3 shows the volumetric data of group FAS and ROU plotted against that of group RES. The linear regression analysis showed strong linear correlation for WM, GM, CSF, BPV, ICV, and MYV ($R = 0.9230$–1.131). A weaker linear correlation was found for NoN ($R = 1.466$, 0.718, respectively). Figure 4 and Figure 5 show Bland-Altman plots for measured brain tissue volumes of groups FAS versus RES and groups ROU versus RES. With the exception of few measurements (≤2 subjects), most of the values fall within the 95% prediction limits.

DISCUSSION

In this study, we comprehensively evaluated the brain synthetic MRI volumetry at various scan times (2 minutes, 29 seconds; 4 minutes, 07 seconds; and 7 minutes, 46 seconds) on healthy volunteers in 3.0-T MRI scanner. Automatic brain segmentation and volume evaluation were performed using synthetic MR software in less than 1 minute. We found that most of the segmented brain tissue volumes and MYV were statistically different among 3 groups (FAS, ROU, RES). The intergroup CVs were less than 7% (except for CSF and NoN), and the linearity was very strong in most of the measured volumes. Bland-Altman plots showed that most of the measurements fall within the 95% prediction limits, which indicated that synthetic MRI with fast imaging protocol can be potentially used to evaluate the brain volumetry for uncooperative patients. However, because using fast synthetic MRI can change the measured brain tissue volumes, it is necessary to use consistent acquisition protocols for comparing or following up cases quantitatively.

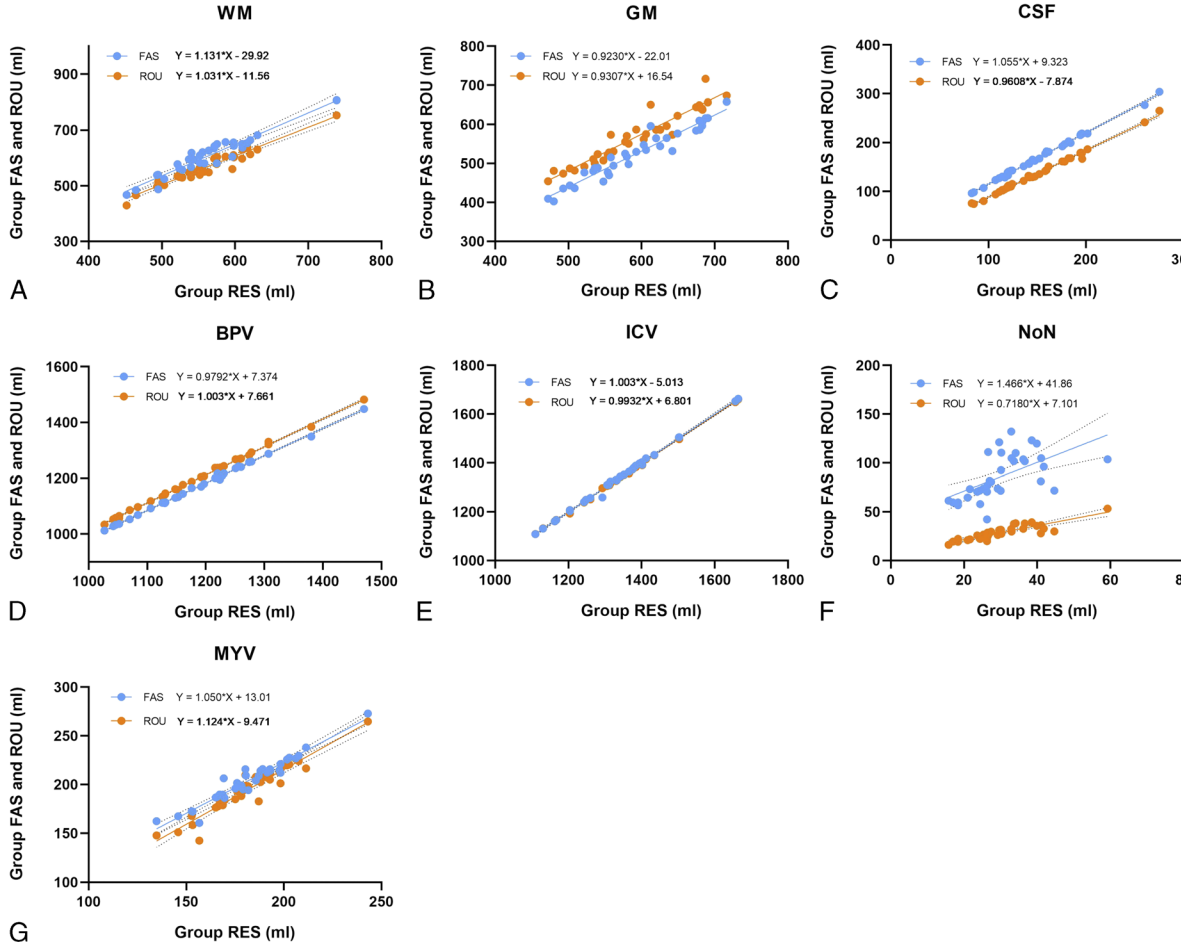

FIGURE 3. Scatterplots showing the linearity of segmented brain tissue volumes and MYVs of volunteers in groups FAS (blue) and ROU (orange) plotted against group RES. Color chart, (A) to (G). Figure 3 can be viewed online in color at www.jcat.org.

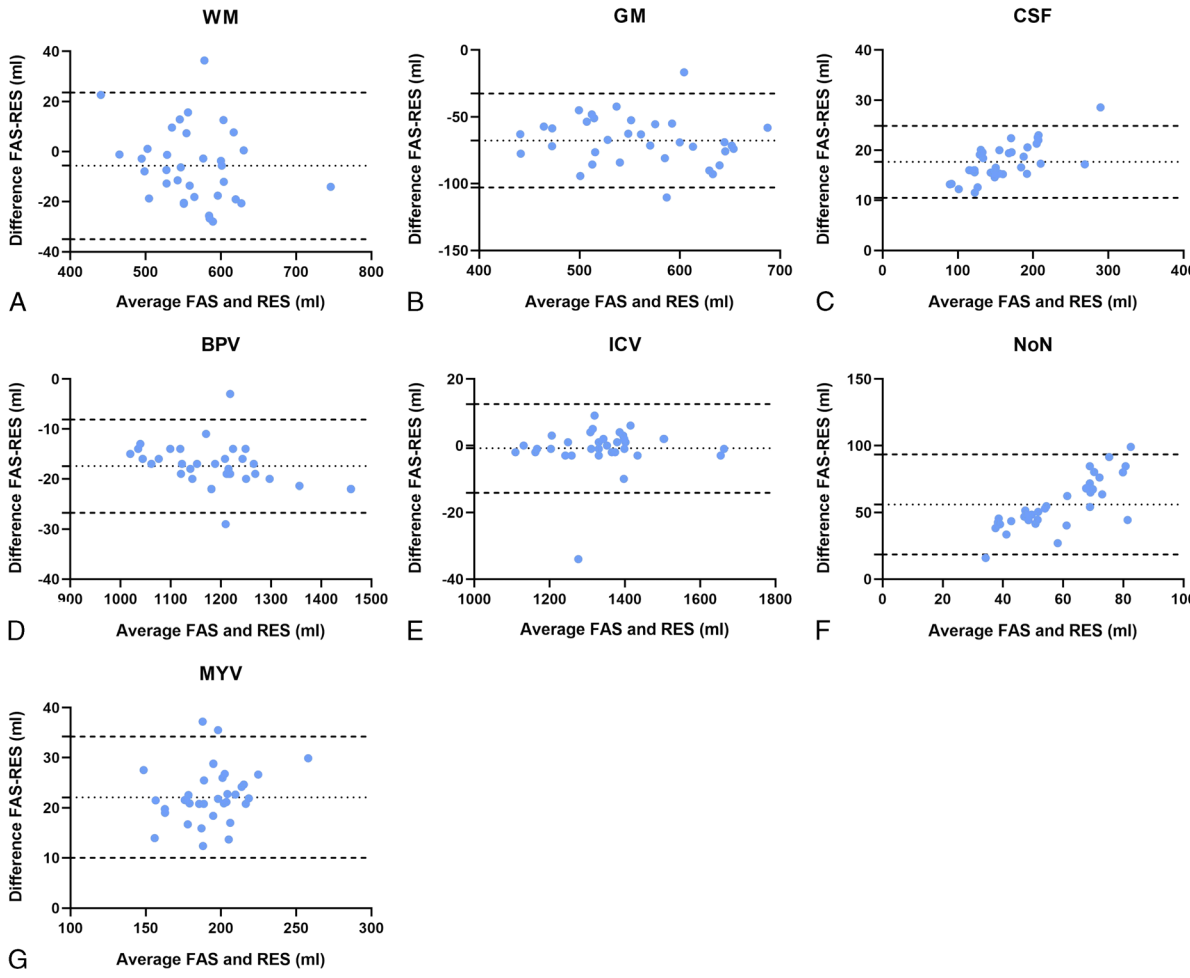

FIGURE 4. Bland-Altman plots showing bias of brain tissue and myelin volumetry of volunteers between groups FAS and RES. Color chart, (A) to (G). Figure 4 can be viewed online in color at www.jcat.org.

With the development of MRI techniques, such as multiband imaging, parallel imaging, and synthetic MRI, it is possible to shorten the scan time while keeping a relatively high imaging quality. Previous studies showed that fast imaging protocols with acquisition time ranging from 3 to 10 minutes demonstrated a practical feasibility for clinical use with uncooperative patients.[21–23] Various in-plane resolutions of synthetic MRI have been used for the brain volumetry evaluation in both 1.5-T and 3.0-T MRI scanner.[12,17] The author concluded that synthetic MRI brain tissue and myelin volumetry with in-plane resolution as low as 1.8 mm can be useful in the evaluation of multiple sclerosis with a short acquisition time of less than 3 minutes in 3.0-T MRI scanner.[12] However, lowering in-plane resolutions results in poorer image quality and can reduce the diagnostic sensitivity. In our study, by modifying several acquisition parameters including matrix, acceleration factor, and echo train length, we shorten the scan time to less than 3 minutes, and the lowest in-plane resolution was 0.8 mm × 1.1 mm, which was much higher than that in previous study.[12] Although we did not evaluate the image quality, contrast images with in-plane resolution of about 1 mm are more practical for clinical use.

In our study, the intergroup CVs of BPV and ICV were very low (less than 1.3%). These may be attributed to the algorithm used in synthetic MRI. Synthetic MRI postprocessing software considers partial volume effect, and multiple tissue compartments with predefined tissue characteristics are allowed in one voxel.[18] The BPV was calculated as the sum of the volumes of WM, GM, and NoN, which have significantly different R1, R2, and PD values from CSF, and the border of the ICV can be clearly outlined with a definition at a PD of 50%. The intergroup CVs of WM, GM, and MYV were less than 7%, which were slightly higher than that of BPV and ICV. These may be attributed to the lower signal-to-noise ratio (SNR) of images in group FAS (Fig. 1). The overall image quality in group FAS was lower, and images were grainier than that in groups ROU and RES. These noises were not recognized as gray or WM, which resulted in the smaller measured GM and WM volumes and larger measured MYV. The intergroup CVs of CSF were larger than 10%, which were higher than that of WM, GM, and MYV. Previous study showed that the T2 measurement of CSF was less reliable because of its very long T2 times,[24] and this may attribute to the variations of CSF volume measurements. Previous comparative study of brain tissue segmentation and volume estimation using synthetic MRI and SPM showed that, although high similarity of volume estimates in GM and WM was demonstrated, the correlation coefficient of CSF volume was relatively low.[16] Therefore, the accuracy of measured CSF volume using fast synthetic MRI is still needed further investigation. The intergroup CV of NoN (67.5%) was the highest one in all the measured volumes, which was in line with the previous study,[24] and the volume of NoN in group FAS was much larger than that of groups ROU and RES. Non-WM/GM/CSF contains tissues that are not categorized as WM, GM, or CSF, and it is

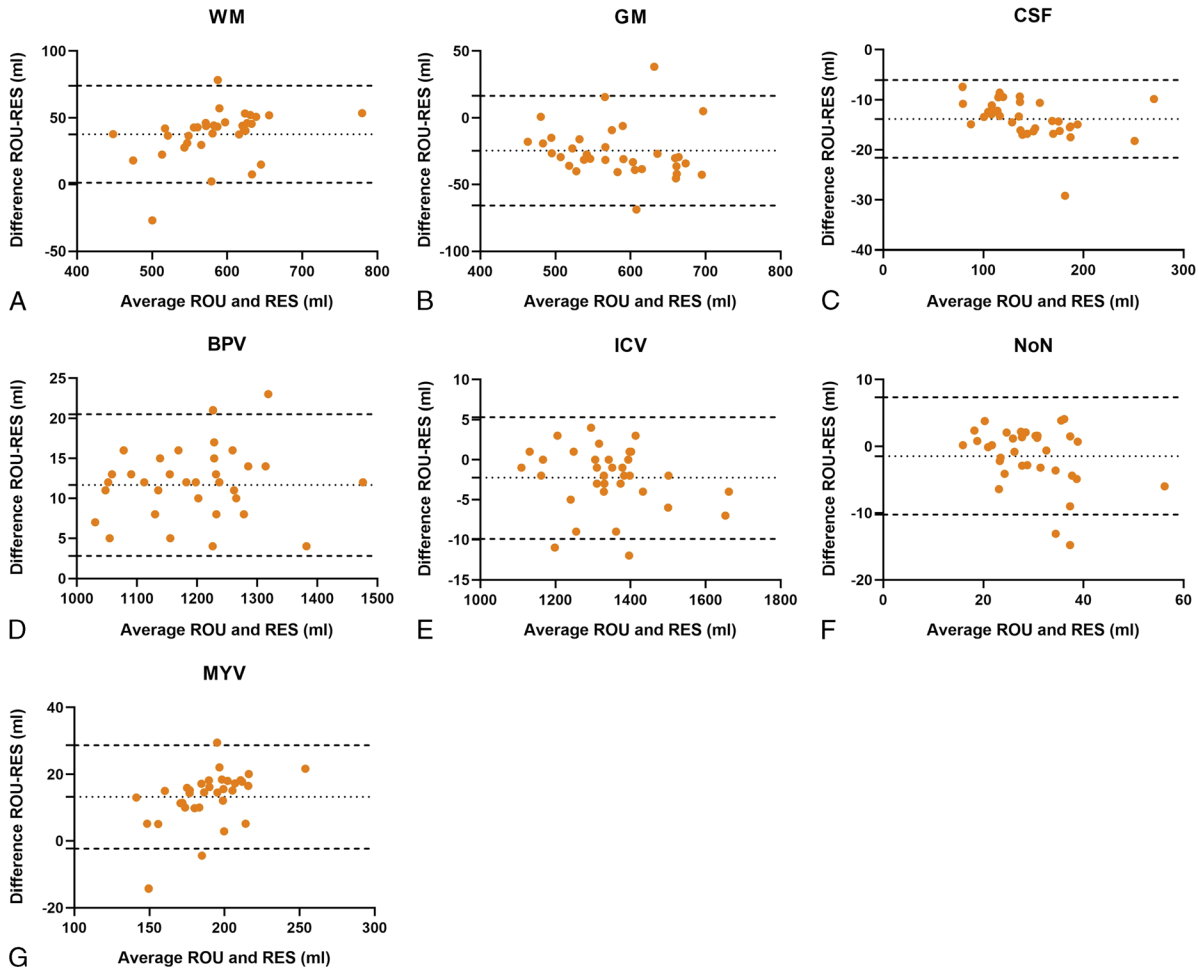

FIGURE 5. Bland-Altman plots showing bias of brain tissue and myelin volumetry of volunteers between groups ROU and RES. Color chart, (A) to (G). Figure 5 can be viewed online in color at www.jcat.org.

calculated from voxels, which is outside the predetermined tissue clusters in R1-R2-PD space.[18] Tissues recognized as NoN are more complex than WM, GM, and CSF, including small elements such as vessels. Therefore, the measured volume of NoN might be affected more prominently by partial volume effects or SNR than that of other brain tissues. Although some bias of measured segmented brain tissue volumes was shown in our study, the linearity was very strong in all the measured volumes (except for NoN).

In our study, the Bland-Altman plots showed that nearly 95% of all the measured data points lied within the 95% prediction limits, and some bias was still existed between the 3 groups. It is important to evaluate the differences at different magnitudes of the measured volumes. The mean bias of −17.4 mL and −0.79 mL was obviously acceptable for BPV and ICV between groups FAS and RES, respectively. For GM volume, the mean bias between groups FAS and RES was −67.7 mL, and the limits of agreement were −103 mL and −32.5 mL, which were larger than that of the other variables. However, the mean difference of 67.7 mL between 2 groups was relatively acceptable for GM volume. The mean bias of measured NoN volume between group FAS and RES was 56.0 mL, and the limits of agreement were 18.5 mL and 93.5 mL, which were too broad compared with the mean NoN volume. This may be related to the variation of image quality between the 2 groups. The overall image quality in group FAS was lower. The noises were more prominent in the cortex region (Fig. 1) and were not recognized as GM but NoN, which resulted in the smaller measured GM volumes and larger NoN volumes. Therefore, bias should be taken into account when evaluating the volumetric measurements using the fast synthetic MRI in clinical practice.

In our study, fast synthetic MRI is achieved by modifying the scanning parameters, and at the same time, it will cause the decrease of SNR, which might result in the bias of measured brain tissue volumes. Deep learning might be a future direction to overcome this challenge. Recent advances in machine learning have been applied to various part of Synthetic MRI workflow. Networks have been designed to reconstruct images with less noise and without loss of resolution. By applying deep learning method to the base images before parameter fitting process, the resulting parameter maps can also exhibit less noise. These advanced reconstruction methods can increase the effective SNR efficiency and can be potentially used to reduce the scanning time as well as further improve the volumetric accuracy with the fast synthetic MRI sequence.[25]

There are some limitations in our study. First, the sample size was relatively small. Second, we did not evaluate the repeatability of the measured brain tissue volumes. In previous study, the repeatability of fast synthetic MRI for measuring T1 and T2 relaxation times of GM, WM, and CSF simulation phantoms was investigated, and high repeatability was revealed for measuring these quantitative values.[26] However, the within-subject reliability has not been

investigated for volunteers. Therefore, further studies are required to validate the repeatability using the synthetic MRI volumetry method. Third, we did not assess the image quality in this study. Although the overall image quality in group FAS was relatively good, further investigation needed to be done to evaluate the diagnostic performance in clinical practice. Fourth, we did not compare the brain tissue volumetry between synthetic MRI method and other current standard segmentation method, such as SPM. However, volumetry results of synthetic MRI have been compared with other MR-based segmentation methods in previous studies, which showed good agreement and repeatability on healthy subjects or patients.[13,16]

In conclusion, we evaluated the automatic brain tissue segmentation and myelin volumetry by synthetic MRI with various acquisition times on 3.0-T MRI scanner. We concluded that using synthetic MRI with fast imaging protocol can change the measured brain tissue volumes of volunteers. It is necessary to use consistent acquisition protocols for comparing or following up cases quantitatively.

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