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Comparison of whole brain segmentation and volume estimation in children and young adults using SPM and SyMRI

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ABSTRACT

Background: MRI brain segmentation and volume estimation of gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) are important for many neurological applications. Signal intensity based measurements, such as the current statistical parametric mapping (SPM) based volume estimation techniques rely on T1W images that involve a series of pre-processing steps, making it impractical for clinical use.
Purpose: In this study, we compared Synthetic MRI (SyMRI) generated relaxometry maps based brain segmentation and estimation of brain volumes with SPM image intensity based segmentation and volume estimation in children and young adults.
Subjects: 176 studies were included for analysis with mean age of 10.9 ± 5.5 years.
Methods: Included studies were quantitatively analyzed and segmented using SyMRI® software. In SPM, the segmentation routine segments brain T1W images into GM, WM, and CSF based on image intensity values. SPM and SyMRI segmentation based volume estimates were plotted. Scatter plots comparing the two methods were generated and agreement was assessed using correlation coefficients.
Results: Correlation coefficient, r, of agreement between the 2 methods was 0.85 for GM, 0.91 for WM, and 0.38 for CSF ($P < 0.0001$ for all three volumes).
Conclusion: Brain imaging in children using SyMRI can identify and calculate estimates of GM, WM, CSF volumes. With our work, we have shown high similarity of volume estimates in GM and WM using SyMRI with a systematic bias for CSF values. The ease of use of this software can make this quantitative data to be used clinically along with the routine anatomical images.

1. Introduction

MRI provides with the opportunity to study brain development within subjects over time. In longitudinal studies, participants can serve as their own control and therefore subtle changes can be identified on an individual level. Quantitative brain image segmentation has the potential to influence the outcomes in clinical studies, especially in pediatric brain imaging [1–3]. It can also help to provide objective data on treatment effects and longitudinal follow-up data on individuals or in clinical trials. Measures of brain volumes have been shown to be valid biomarkers of clinical state and pathology progression, especially on patients referred for evaluations of microcephaly, macrocephaly, or hydrocephalus [4]. On visual assessment, brain atrophy is recognized by increase in CSF space and shrinkage of parenchymal structures. The role of quantitative volumetric assessment is complementary to that of visual assessment with the specific aim of improving the detection of focal and subtle brain pathology. Quantitative information extraction from cerebral MR images relies on reliable and consistent brain tissue segmentation software. Currently available popular and commonly used segmentation methods, such as Statistical Parametric Mapping (SPM), rely on signal intensity based differentiation of tissue types and involve a series of pre-processing steps and age based atlas based templates [5–8]. The choice of pre-processing steps and user dependent associated parameters can influence brain segmentation measurements [9]. Another drawback with the current SPM based method is that it typically requires high resolution 3D isotropic anatomical images and is relatively time consuming [10]. This method is commonly used in the research community but in its current stage is impractical for routine clinical use. A new technique of segmenting brain tissue is available using MRI based relaxometry maps (SyMRI, Synthetic MR, Linkoping, Sweden) [11,12]. SyMRI is a synthetic MR imaging method based on a quantitative approach in which a specific sequence (MDME, a multiple-

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spin echo multi-saturation recovery sequence) allows for simultaneous measurements of absolute R1 relaxation rate (1/T1), R2 relaxation rate (1/T2), and proton density (PD) [3,11,12]. Using these measurements, synthetic MR images can be generated by calculating pixel values based on user-defined settings of echo time (TE), repetition time (TR), and inversion time (TI) [13,14]. The dedicated SyMRI software uses combinations of R1 and R2 values to segment intracranial volume (ICV), gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) [3,15] using a relatively easy to apply user-friendly software interface. In addition, SyMRI also allows the generation of multiple synthetic image contrasts from a single scan acquisition (e.g. T1, T2, FLAIR) [13,14]. This can result in MRI scan time savings as compared to conventional imaging and in pediatric imaging may result in less anesthesia and sedation time. The purpose of this study was to compare SyMRI relaxometry based segmentation and estimation of brain volumes with traditional signal intensity based SPM segmentation as an initial step in understanding the utility of SyMRI for research and clinical applications in children.

2. Methods

2.1. Study population for data acquisition

An IRB approved retrospective review was performed of all brain MR examinations over a 34 month period in which the MDME sequence was performed. Patients undergoing routine brain MRI studies on two scanners capable of performing the quantitative MDME MR sequence (as an add on sequence) during the evaluation period were included. Studies with excessive patient motion, excessive artifact from dental or medical devices, and age over of 21 years were excluded. Clinical exclusion criteria were applied to define a population with normal imaging and excluding those with clinical diagnoses or medications potentially affecting intracranial tissue volumes as previously described [3].

2.2. Imaging sequence

Exams were performed on either a 3 T GE 750 W (GE Healthcare, Waukesha, USA), 1.5 T GE 450 W (GE Healthcare, Waukesha, USA), or a 1.5 T Philips Ingenia (Philips Healthcare, The Netherlands) scanner as part of routine clinical care. Two sequences were assessed for this study:

1. MDME sequence: Acquired utilizing four different saturation delay times (140, 540, 1870, and 3870 ms at a TR of 4000 ms) and two TEs (21 and 94 ms). The scan time for acquisition was approximately 6 min [11,12].
2. 3D volumetric T1W sequence: Acquired with a TR/TE/TI = 6.7/3.1/450 ms; FA = 12°; FOV = 25.6 cm; Matrix size = 256 × 256; Acceleration factor = 2; NEX = 1. No fat saturation was applied. The scan time was approximately 4 min.

Abbreviations: TR: relaxation time, TE: echo time, TI: inversion time, ms: milliseconds, FA: flip angle, FOV: field of view, NEX: number of excitations.

2.3. Image post-processing by SyMRI

Synthetic MRI (SyMRI®) is a quantitative MRI method in which a multiple-spin echo saturation recovery sequence (MDME) is used to measure absolute R1, R2 and PD [16]. Fully automated synthetic MRI visualization software loads the raw DICOM data; performs relaxivity curve fitting to the Bloch equations and calculates whole brain R1, R2, and PD maps used to synthesize MRI images with standard contrast. Additionally, the R1, R2, and PD maps are used as inputs to calculate an intracranial mask, that determines the ICV. A look up table is used to convert R1, R2, and PD values of each voxel into tissue volume fractions with no atlas, manual tracing, or a priori assumptions of tissue distribution or anatomy. Whole intracranial volumes of CSF, GM, WM, are calculated by summing the partial volume fraction of each voxel within the ICV. The partial volume method accounts for voxels containing multiple tissue types and decreases dependence on the acquired resolution of the dataset. A key advantage of this segmentation method is that unlike voxel intensity in standard MRI images; R1, R2, and PD values are inherent physical properties of a given tissue/voxel at a given field strength, and are otherwise independent of the acquisition strategy or hardware. Processing time for each case was approximately 10 to 30 s.

2.4. Image post-processing by SPM

SPM is a Matlab based software package implementing statistical methods for analysis and segmentation of functional and structural neuroimages [10]. For SPM based segmentation, 'default segmentation' technique using unified segmentation algorithm in SPM ver. 8 was used to allow for infant templates for infant data until age of 15 months [17] and 'new segmentation' using updated unified segmentation algorithm in SPM ver. 12 was used for images of subjects with age > 15 months [18,19]. This segmentation technique is based on the method that utilizes a combined pixel intensity and a priori knowledge approach using a prior probability template for GM, WM and CSF to make an initial probability estimate as to which tissue type a voxel most likely belongs to and then proceeds to do a cluster analysis with a modified mixed model [20]. The software performs tissue segmentation, registration and intensity non-uniformity (bias) correction all in the same model. SPM segments the input MR image into GM, WM, and CSF.

SyMRI based segmentation is based on relaxometry values and SPM based segmentation is based on image intensity values [3,12,20]. SyMRI based segmentation was done by S.D.S and SPM based segmentation was done by J.D. Both readers were blinded to each other's segmentation measurements.

2.5. Statistical tests

Statistical analyses were performed using MedCalc (MedCalc ver. 18.2, Ostend, Belgium). Continuous variables were presented as mean ± standard deviation (SD) and categorical variables as percentages and counts. Volume estimates measured using the two techniques were compared and agreement was assessed using correlation coefficients. The values were compared using interclass correlation with a P-value < 0.05 considered statistically significant. Bland-Altman difference plots were generated to assess the agreement between the volume measurements by both methods. Scatter plots were generated to display the 95% prediction limits for the two datasets.

3. Results

176 MRI examinations were included for analysis (107 females and 69 males) with mean age of 10.9 ± 5.5 years (range: 0.1 to 21 years). A representative image of segmentation by both methods is shown in Fig. 1. SPM and SyMRI segmentation based volume estimate plots plotted versus patient age are shown in Fig. 2 (A, GM vs Age. B, WM vs Age. C, CSF vs Age). SyMRI based WM and GM volume estimates overlap well with SPM based volumes (Table 1). SyMRI based CSF volume estimates are consistently lower than SPM based estimates. Scatter plots comparing the two methods are shown in Fig. 3 (A, GM measured with SPM vs SyMRI. B, WM measured with SPM vs SyMRI. C, CSF measured with SPM vs SyMRI). With the exception of few (< 10 subjects) borderline outliers, all values fall within 95% prediction limits. Correlation coefficient, r, of agreement between the two methods was 0.85 (95% CI: 0.81–0.88) for GM, 0.91 (95% CI: 0.87–0.93) for WM, and 0.39 (95% CI: 0.25–0.50) for CSF ($P < 0.001$ for all three volume estimates) (Table 2). Bland-Altman difference plots

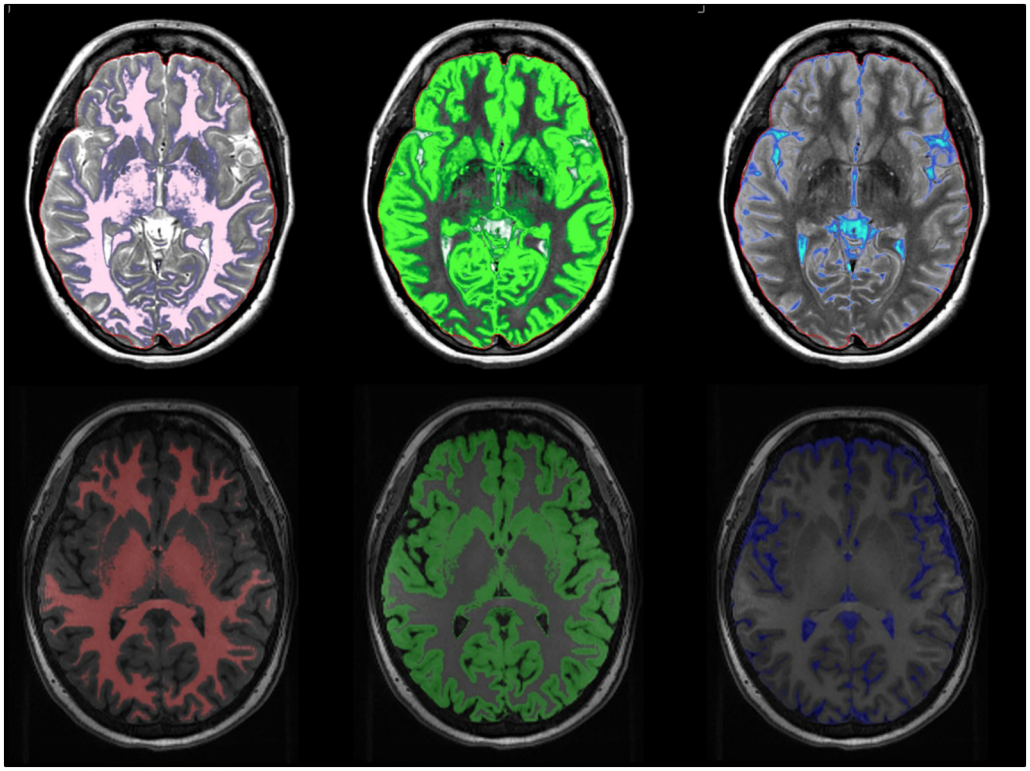

Fig. 1. Representative slice segmentation results of a 17 year old male subject. WM, GM and CSF image using SyMRI segmentation (top row) and SPM (bottom row).

for the two methods show a mean bias of −39.9 ml for GM, −16.0 ml for WM and +298.2 for CSF (Fig. 4). With the exception of few (< 10 subjects) borderline outliers, all values fall within two standard deviations. While it was significant, correlation between CSF volumes was much less than for other components.

4. Discussion

Brain segmentation and volume estimation are important for pediatric clinical neurological studies and has many clinical applications from measuring and visualizing these tissues and their pathological changes to surgical planning and image-guided interventions [21]. Also, volumetric changes are routinely observed in normal pediatric brain growth [3]. Qualitative assessments are routinely done by pediatric neuroradiologists however a reliable, rapid method of quantitative measurements is needed for accurate individual follow-up as well as quantitative comparison with reference groups.

Traditionally brain segmentation (extracting GM and WM) from MRI anatomical images is a time-consuming step in neuroimaging research making it challenging and impractical for routine clinical use. Various methods for brain segmentation have been described and are available. Among them, commonly used software's include SPM developed by University College, London, UK; FMRIB Software Library (FSL) developed by Oxford center for functional MRI of the brain, Oxford, UK; BrainSuite written by University of California Los Angeles, CA, USA and FreeSurfer developed by Martinos Center for Biomedical Imaging, Massachusetts, USA. Although numerous image intensity based brain segmentation methods have been developed, used and compared with one and another, SPM based methods have been shown to have slightly higher sensitivity and are commonly used [19]. At our large tertiary care dedicated pediatric institute, SPM methods are routinely used to develop, collaborate and promote the availability of pediatric atlas based templates for research purposes [20]. However, in general, MRI segmentation for routine clinical use is still not a trivial task because segmentation software that use image intensity template based approach need to correct for imperfections due to noise and other image artifacts. The process involves a series of pre-processing steps that has its challenges [22,23]. New faster and user-friendly methods for brain MRI segmentation continue to emerge and are being explored.

The goal of this study was to evaluate the performance of relaxation based SyMRI software for brain segmentation and compare it to traditional SPM based segmentation methods. Unlike other methods that require performing pre-processing steps, SyMRI allows for automated segmentation based on relaxivity and without the need for any pre-processing steps or age based template information.

The very strong correlation of SyMRI derived GM and WM segmentation values in comparison to SPM is encouraging suggesting that SyMRI based method can be used for clinical and research purposes with comparable values. SyMRI based volume measurements have been shown to have a coefficient of variation of 1.4% and 1.8% for GM and WM respectively [21]. CSF segmentation using image intensity based method is challenging due to partial volume effects and other bright anatomical structures such as fat and bone. The low correlation coefficient of CSF measurement is probably due to partial volume effect and the known inefficiency of SPM to accurately measure CSF volume based on signal intensity [22,24]. In addition, the two methods follow different skull stripping algorithms, which could influence CSF segmentation. Despite significant correlation between CSF volumes provided by the two methods, there are substantial absolute differences with SyMRI mean CSF being approximately 300 ml less than SPM. The estimates provided by SPM are likely overestimated given the normal total CSF volume in humans of around 100–150 ml. Therefore, the lower values provided by SyMRI may be more physiologically accurate based on experimental estimates of CSF volume in humans.

In a previous prospective study on 20 adult patients with Multiple-Sclerosis with a mean age of 44 years and 20 healthy controls with a mean age of 41 years comparing volumetric measurements by SyMRI using a similar acquisition method vs other conventional methods such as FreeSurfer, SPM, and FSL on a single Siemens 3 T MRI scanner; the authors report that SyMRI software provided volumetric measurements

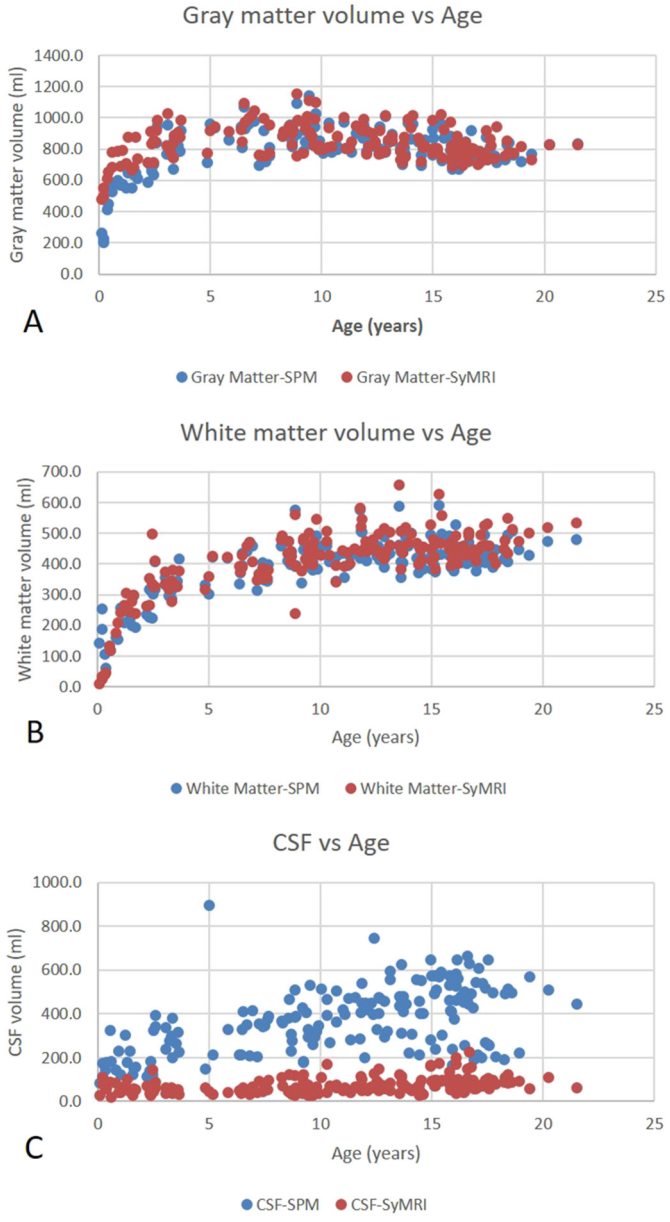

Fig. 2. SPM and SyMRI segmentation based volume estimate plots plotted versus patient age. (A) GM vs Age, (B) WM vs Age, and (C) CSF vs Age.

Table 1
Comparison of segmented brain volumes.

	GM	WM	CSF
SyMRI	835.2 ± 105.8	412.9 ± 104.2	73.6 ± 35.9
SPM	796.4 ± 135.4	396.9 ± 91.1	371.8 ± 149.6

Volumes (ml) are presented as mean ± standard deviation.

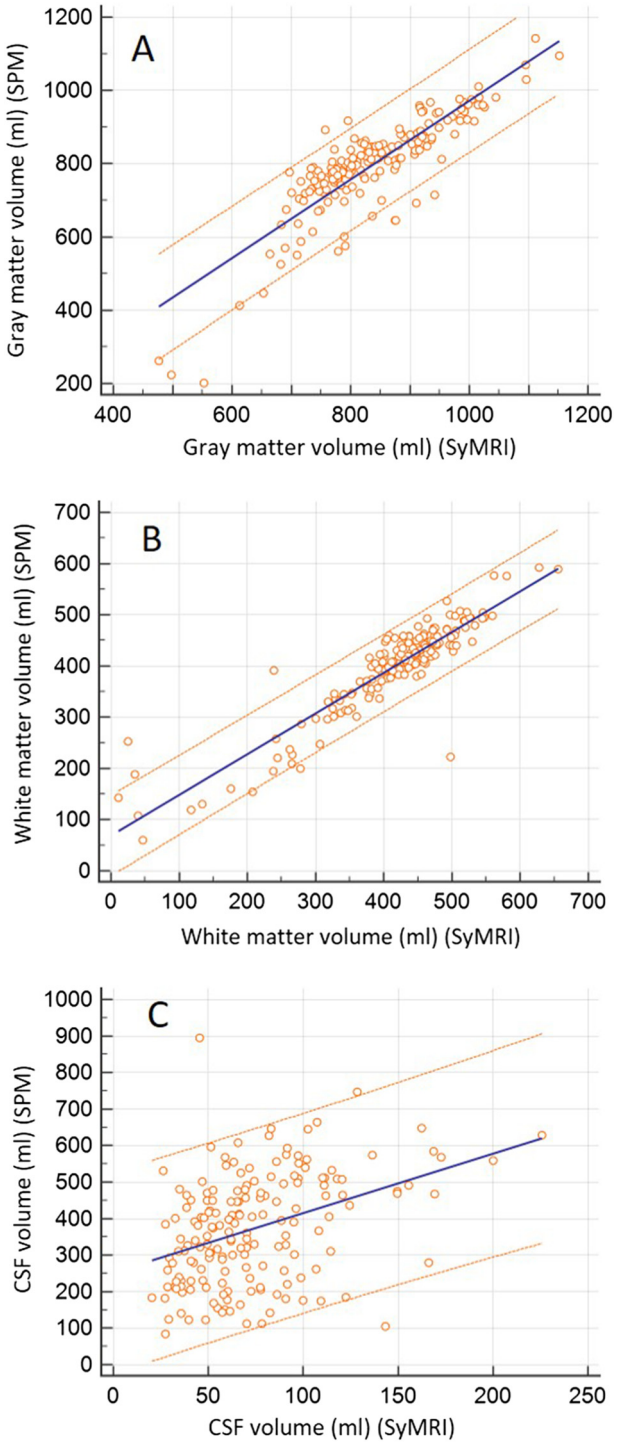

Fig. 3. Scatter plots comparing the two methods. (A) GM measured with SPM vs SyMRI, (B) WM measured with SPM vs SyMRI, and (C) CSF measured with SPM vs SyMRI. Coefficient of agreement between the 2 methods: $r = 0.85$ (95% CI: 0.81–0.88) for GM, $r = 0.91$ (95% CI: 0.87–0.93) for WM, and $r = 0.39$ (95% CI: 0.25–0.51) for CSF ($P < 0.0001$ for all 3 volumes).

in the same order of magnitude as the 3 commonly used volumetric software programs [25]. Our results confirm these findings and provide further evidence that volumes measured using SyMRI are in agreement with SPM in the pediatric population.

Our study has limitations. Results obtained via SPM based analysis may differ based upon operator differences and thresholding settings. We used single experienced operator to perform the segmentation to minimize the error as much as possible. The MDME sequence and volumetric T1 sequence differ significantly in slice thickness, although despite this there was very close agreement of parenchymal segmentation volumes. SYMRI is thought to overestimate GM segmentation in infants and very young children related to incomplete myelination [3] however the nearly identical results with SPM point to a similar estimation issues. All imaging based GM, WM, and CSF measurements are made without the knowledge of ground truth. Our intent was not to assess true quantitative accuracy but to compare a new segmentation method (SyMRI) versus a traditional popularly used

Table 2
Statistical summary of segmented brain volumes compared between both methods.

	GM	WM	CSF
Correlation coefficient, r	0.85 (95% CI: 0.81–0.88)	0.91 (95% CI: 0.87–0.93)	0.39 (95% CI: 0.25–0.50)
Pearson's precision, ρ	0.85	0.91	0.39
Concordance correlation	0.79 (95% CI: 0.74–0.84)	0.89 (95% CI: 0.85–0.91)	0.04 (95% CI: 0.02–0.05)

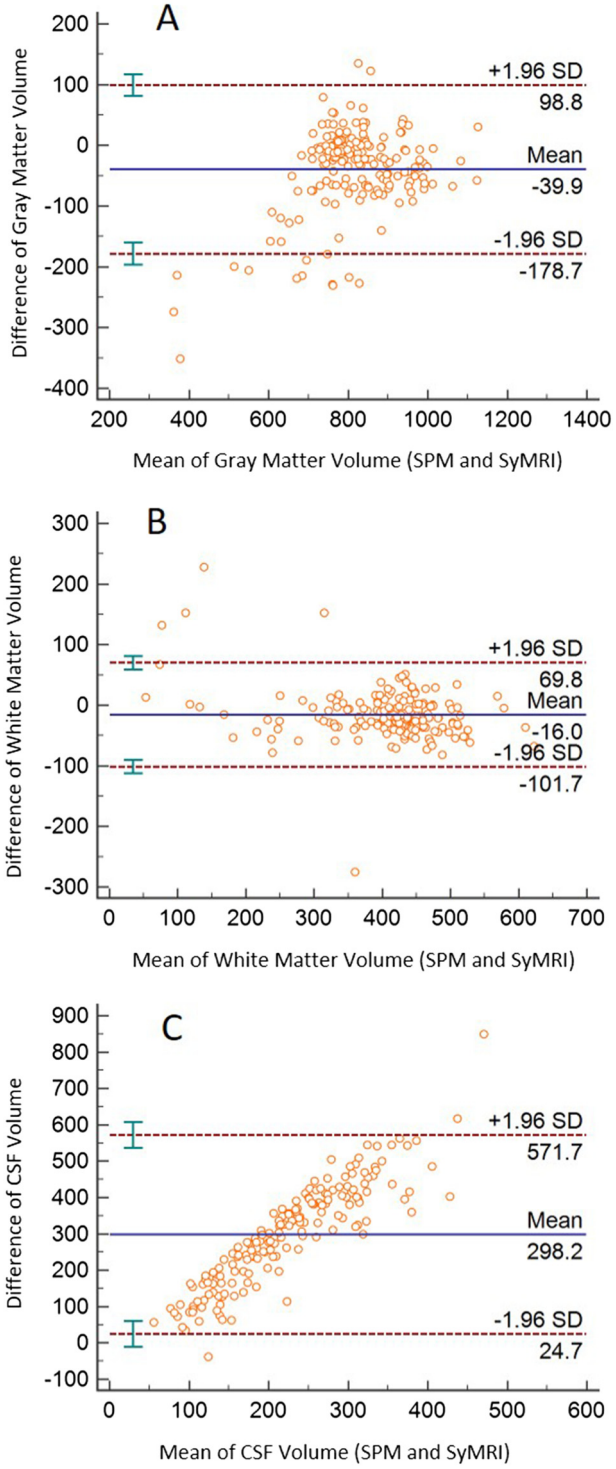

Fig. 4. Bland-Altman difference plots between SPM and SyMRI. (A) GM, (B) WM, and (C) CSF.

method (SPM). MRI scans were done on patients referred for clinical purposes and may not be a reflective of 'normal' and 'healthy' population. However, by following a strict exclusion criteria, we minimized the influence of 'abnormal' studies and included 'clinically normal' and 'healthy' brains. Future large scale, multi-vendor MRI platform and multi-center studies on healthy and diseased patient population may be helpful to validate our observations.

5. Conclusion

To date, brain volume measurements requires the use of complex template based software. Using an in-line software makes the use of volumes available in routine clinical practice. SyMRI is a promising new relaxometry based imaging technique. Whole brain mapping in children using SyMRI can rapidly identify and calculate estimates of GM, WM, CSF volumes. GM and WM estimates agree well with SPM analyses, a common tool for brain segmentation, typically requiring more processing expertise and time for assessment.

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