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Automated quantification of deep grey matter structures and white matter lesions using magnetic resonance imaging in relapsing remission multiple sclerosis

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Abstract

Background: Brain volume loss (BVL) is widespread in MS and occurs throughout the disease course at a rate considerably greater than in the general population. In MS, brain volume correlates with and predicts future disability, making BVL a relevant measure of diffuse CNS damage leading to clinical disease progression, as well as serving as a useful outcome in evaluating MS therapies. The aim of our study was to evaluate the role of automated segmentation and quantification of deep grey matter structures and white matter lesions in Relapsing Remitting Multiple Sclerosis patients using MR images and to correlate the volumetric results with different degrees of disability based on expanded disability status scale (EDSS) scores.

Results: All the patients in our study showed relative atrophy of the thalamus and the putamen bilaterally when compared with the normal control group. Statistical analysis was significant for the thalamus and the putamen atrophy (*P* value < 0.05). On the other hand, statistical analysis was not significant for the caudate and the hippocampus (*P* value > 0.05); there was a significant positive correlation between the white matter lesions volume and EDSS scores (correlation coefficient of 0.7505). On the other hand, there was a significant negative correlation between the thalamus and putamen volumes, and EDSS scores (correlation coefficients < − 0.9), while the volumes of the caudate and the hippocampus had a very weak and non-significant correlation with the EDSS scores (correlation coefficients > − 0.35).

Conclusions: The automated segmentation and quantification tools have a great role in the assessment of brain structural changes in RRMS patients, and that it became essential to integrate these tools in the daily medical practice for the great value they add to the current evaluation measures.

Keywords: Multiple sclerosis, MRI volumetry in RRMS, Brain volume loss

Background

Multiple sclerosis (MS) is a chronic neurological disease of the central nervous system (CNS) characterized pathologically by inflammation, demyelination, inadequate repair, gliosis, and neuronal/axonal degeneration. It has no known cause, unpredictable progression, and no known cure. The symptoms vary between individuals and with disease course and may include visual disturbances, mobility problems, coordination problems, extreme fatigue, loss of balance, muscle stiffness, speech problems, bladder and bowel problems, memory problems, and partial or complete paralysis [1].

According to the MS International Federation (MSIF), it affects approximately 2.3 million people worldwide [2]. The average age of diagnosis is 30 years [3, 4]. MS affects

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at least twice as many women as men [5] and is the most common neurological disease affecting young adults [6].

Relapsing Remitting Multiple Sclerosis (RRMS) is the most common subtype affecting about 87% of patients diagnosed with MS. It is characterized by episodic exacerbations, or "attacks", during which symptoms develop over a few days, remain for several weeks or months, and then resolve either completely or partially. If residual symptoms remain, they remain stable until the next exacerbation [7].

The clinical disability in MS patients can be quantified using the expanded disability status scale (EDSS) developed by Kurtzke [8]. The EDSS is based on a neurological examination quantifying disability in eight Functional Systems (FS) by assigning a functional system score (FSS) [9].

Isotropic, high-resolution T1-weighted (T1-W) and fluid attenuated inversion recovery (FLAIR) 3D volumetric acquisitions are best able to detect the small changes which occur over time. This is usually measured as changes in brain structures volumes and WM lesions volumes [10].

The new automated and semi-automated post-processing techniques done by advanced software packages like Oxford Center for Functional MRI of the Brain (FMRIB), Software Library (FSL) [11, 12], and Lesion Topology-preserving Anatomical Segmentation (Lesion-TOADS) [13] allowed a streamlined process of segmenting and quantifying various deep grey matter structures as well as white matter lesion.

The aim of the current study was to evaluate the role of automated segmentation and quantification of deep grey matter structures and white matter lesions in Relapsing Remitting Multiple Sclerosis patients using MR images and to correlate the volumetric results with different degrees of disability based on EDSS scores.

Methods

Study design and population

This prospective study was carried on 31 patients (case group/group I) previously diagnosed with RRMS by clinical examinations and conventional MRI according to modified McDonald's criteria and referred to diagnostic radiology department from the neurology department throughout period extending from December 2017 to March 2020 for further MRI assessment; 31 healthy control (HC) subjects (control group/group II) of both sexes were selected amongst relatives or caregivers of the studied patients with age and sex distribution similar to case group with no medical or neurological disorders.

Exclusion criteria: general contraindications for MRI scan, for example, patients with claustrophobia, patients who have a cardiac pacemaker or a metallic prosthesis or bad general condition, also patients who refused to be included in our study.

Ethics committee approved, and informed consent was obtained for all patients or their guardians. Privacy and confidentiality of all patients data were guaranteed; all data provision were monitored and used for security purpose only.

Preparation and protocol

All subjects were subjected to

1. Full history taking and thorough clinical examination
2. The expanded disability status scale (EDSS) was done for all subjects. Scores can quantify the disability in MS patients in eight functional systems (FS) by assigning a functional system score (FSS) in each of these functional systems [8].
3. Clinical, neurological, and psychological examinations were done by trained and qualified clinicians in the neuropsychiatry department established the diagnosis of MS through history taking and using 2017 McDonald MS Diagnostic Criteria [14].
4. Neuroimaging

Brain MRI was performed on a 1.5 T GE Signa (General Electric, Milwaukee, WI, USA) closed-configuration whole-body scanner using a standard quadrature head coil.

All patients were subjected to the following protocols:

(I)MRI scanning

Sagittal 3D T1-weighted spoiled gradient (SPGR) and sagittal cube T2 FLAIR utilizing the following parameters in Table 1.

(II) Image analysis

Subcortical structures and white matter lesions segmentation and quantification.

(a) Fully automated post-processing analysis of the 3D T1-W MRI data was done using FSL software package version 5.0.10. Semi-automated segmentation and quantification of white matter hyper-intensity lesions in the 3D T2 FLAIR sequence were done. The post-processing steps included:
(b) Rigid linear registration of the acquired T1W images (subcortical structures) and of the acquired 3D T2 FLAIR images (white matter hyper-intensity lesions) for every subject to the Montreal Neuroimaging Institute template dataset (MNI 152) with 1 mm × 1 mm × 1 mm reconstruction matrix, was done to transform all subjects data to a standard space which allowed group-level analysis of the

Table 1 Detailed imaging parameters used for acquiring 3D T1W and Cube T2 FLAIR sequences

Imaging parameters	3D T1W SPGR	Cube T2 FLAIR
Plane	Sagittal	Sagittal
Mode	3D	3D
Prep. time	500 ms	–
Inversion time	–	1990 ms
TE	Minimum full	115 ms
TR	7.2 ms	7600 ms
FOV	256 × 256 mm	240 × 240 mm
Phase FOV	1.0	1.0
Slice thickness	1.2 mm	1.4
Number of slices	160	140
Slice spacing	Zero	Zero
Matrix	192 × 192	256 × 256
Flip angle	10°	–
Frequency	16 kHz	41.67 kHz
Frequency direction	S/I	S/I
NEX	1.0	1.0
Shim	Auto	Auto
Phased array uniformity enhancement (PURE)	On	–
Surface coil intensity correction (SCIC)	Off	Off

quantified results. This was done using the (FSL-FLIRT) pipeline of the software package.

(c) Automated segmentation of the subcortical grey matter structures (thalamus, caudate, putamen and hippocampus) was done using a subset pipeline of the software called "FSL-FIRST" which utilizes model-based registration/segmentation methods based on manually segmented images provided by the Center for Morphometric Analysis (CMA), MGH, Boston [11, 12]. Automated segmentation of white matter hyperintense lesions using Lesion-TOADS tool which is a part of MIPAV software package version 7.4.0 [13]. The output of the segmentation was visually inspected for errors of segmentation and missed lesions which was then corrected manually to get accurate quantitative results.

(d) Measuring the volumes of each structure on both sides and the volumes of white matter hyper-intensity lesions was done using (FSL-STATS) pipeline of the software package; then, the volumes of each subcortical structure on both sides were compared to age-matched normal control to detect any volumetric changes, and then, Pearson correlation coefficient was calculated to correlate between the volumes of subcortical structures & white matter hyper-intensity lesions and EDSS scores.

Table 2 Distribution of age of the studied patients and control groups

Age groups	No. of patients	%	No. of control	%
20–< 25	13	41.9%	14	45.1%
26–< 30	8	25.8%	9	29%
31–< 35	10	32.3%	8	25.8%
Total	31	100%	31	100%
Min.–Max	20–35		20–35	
Mean ± SD	27.54 ± 4.93		25.94 ± 4.89	

(III) Image interpretation

The interpretation of the images was done by two expert radiologist who had experience in neuroradiology 10 and 6 years.

(IV) Statistical analysis of the data

- Data were fed to the computer and analysed using IBM SPSS software package version 20.0.
- Qualitative data were described using number and percent.
- Quantitative data were described using range (minimum and maximum), mean, and standard deviation.
- Comparison of volumetric quantitative findings with normal values was done using one sample *z* test.
- Pearson correlation coefficient was calculated to test the correlation between the volumetric findings (including deep grey matter structures and white matter lesions volumes) and EDSS scores.
- Significance test results are quoted as two-tailed probabilities. Significance of the obtained results was judged at the 5% level; *P* values > 0.05 or < 0.05.

Results

Demographic data

The study included 31 patients diagnosed with RRMS (group I); the age ranged between 20 and 35 years with mean age of 27.54 ± 4.93 years and 31 healthy control subjects (group II) of the same age range and a mean age of 25.94 ± 4.89 years (Table 2). As regards the sex distribution of the studied patients group, 25.8% of them were male patients and 74.2% of them were female. On the other hand, 35.5% of the control group were male subjects and 64.5% were female.

The patients group had EDSS score ranging from 1 to 6.5 with a mean score of 3.64 and a standard deviation of 1.39. Seven subjects had EDSS scores ranging from 1

to 2.5, seventeen had scores ranging from 3 to 4.5, and the final seven subjects had scores ranging from 5 to 6.5 (Table 3).

Volume of the thalamus (Table 4)

The values of estimated volume of the thalamus relative to the total intracranial volume on both sides showing significant decrease in the RRMS group compared to the control group with a Z score of -2.17152 (P value < 0.05) for the left thalamus and a Z score of -2.822 (P value < 0.05) for the right thalamus.

Volume of the caudate, putamen, and hippocampi (Table 5)

The values of estimated volume of the caudate, putamen, and hippocampi relative to the total intracranial volume on both sides didn't show any significant difference between the RRMS group and the control group.

Volume of white matter lesions (Table 6)

The semi-automated segmentation and quantification of white matter lesions of the studied patient group showed that 41.9% had less than 4 mm^3 of white matter lesions, 35.4% had lesion volumes ranging from 4 to 10 mm^3, and the remaining 22.7% had lesion volumes more than 10 mm^3. The mean white matter lesion volume was 6.62 mm^3, and the standard deviation was 5.71 mm^3 with a minimum volume of 1.7 mm^3 and a maximum volume of 27.4 mm^3.

Table 3 Distribution of EDSS scores of the studied group

EDSS scores	No	%
1–2.5	7	22.5%
3–4.5	17	55%
5–6.5	7	22.5%
Total	31	100%
Min.–Max	1–6.5	
Mean ± SD	3.64 ± 1.39	

Correlation between subcortical structures volumes, white matter lesions volumes, and EDSS scores

We were able to divide our studied patient group into 3 subgroups based on their EDSS scores:

- The 1st subgroup had 7 patients (22.5%) with EDSS scores ranging from 1 to 2.5. This group had a significant but mild atrophy of the thalamus. They also had a smaller volume of white matter lesions.
- The 2nd subgroup had 17 patients (55%) with EDSS scores ranging from 3 to 4.5. This group had a significant moderate atrophy of the thalamus and putamen. They had a larger volume of white matter lesions.
- The 3rd subgroup had 7 patients (22.5%) with EDSS scores ranging from 5 to 6.5. This group had the most significant and most severe atrophy of the thalamus and putamen with atrophy patterns starting to affect other deep grey matter structures, mainly the hippocampus. This subgroup had the largest volume of white matter lesions.

According to this distribution and after calculating the correlation coefficients of the volumetric measures with the EDSS scores, we found that the volumes of the thalamus and putamen were negatively correlated with the EDSS scores (Figs. 1 and 2) with correlation coefficients < -0.9 and significant P values < 0.05, while the volumes of the caudate and the hippocampus had a very weak and non-significant correlation with the EDSS scores (Figs. 3 and 4) having correlation coefficients > -0.35 and non-significant P values > 0.05.

On the other hand, we found that white matter lesion volumes were strongly correlated with the EDSS score (Fig. 5) with a correlation coefficient of 0.7505 and significant P value < 0.05.

Table 4 Quantitative results of the left and right thalami, including absolute volumes, volumes after correction for ICV, Z scores and P values

Thalamus	Cases ($n = 31$)	Control ($n = 31$)	Z scores	P values
Left				
Min.–Max	4028–6794	6735–10,726	**−2.17152**	**0.029931**
Mean ± SD	5442 ± 680	8281 ± 1032		
After correction for ICV	0.003838	0.005231374		
Right				
Min.–Max	2189–6889	6738–10,845	**−2.822**	**0.004773**
Mean ± SD	4482 ± 926	8183 ± 1069		
After correction for ICV	0.00313	0.005174751		

Bold values indicate the significant Z-scores (< -2) and significant P-values(< 0.05)

Table 5 Quantitative results of the left and right caudate, putamen, and hippocampi

	Cases ($n=31$)	Control ($n=31$)	*Z* scores	*P* values
Left caudate				
Min.–Max	2511–4621	2831–4806	0.31159	0.755421
Mean ± SD	3452 ± 476	3672 ± 488		
After correction for ICV	0.002417	0.002321		
Right caudate				
Min.–Max	2441–5078	2946–4872	0.354	0.723339
Mean ± SD	3567 ± 540	3773 ± 473		
After correction for ICV	0.002497	0.002387		
Left putamen				
Min.–Max	1854–4927	4217–6918	**− 2.08832**	**0.036798**
Mean ± SD	3704 ± 707	5346 ± 603		
After correction for ICV	0.002593	0.003379		
Right putamen				
Min.–Max	1322–5084	4239–6701	**− 2.29**	**0.022021**
Mean ± SD	3606 ± 770	5330 ± 589		
After correction for ICV	0.002524	0.003369		
Left hippocampus				
Min.–Max	2938–4860	3327–5062	− 0.1508	0.880765
Mean ± SD	3703 ± 355	4170 ± 412		
After correction for ICV	0.002592	0.002642		
Right hippocampus				
Min.–Max	2580–4710	3340–5695	− 0.094	0.925109
Mean ± SD	3834 ± 421	4291 ± 462		
After correction for ICV	0.002684	0.002719		

Bold values indicate the significant *Z*-scores (< -2) and significant *P*-values(< 0.05)

Table 6 White matter lesions volumes distribution in the studied patients group

Lesion volumes (cm^3)	No. of patients	%
< 4	13	41.9%
4–10	11	35.4%
> 10	7	22.7%
Total	31	100%
Min.–Max	1.7–27.4	
Mean ± SD	6.62 ± 5.71	

Discussion

Multiple sclerosis is an inflammatory demyelinating and neurodegenerative disease of the central nervous system [15–17]. In MS, brain volume correlates with and predicts future disability [18, 19], making brain volume loss a relevant measure of diffuse CNS damage leading to clinical disease progression, as well as serving as a useful outcome in evaluating MS therapies [20, 21].

The use of automated methods for segmentation of deep GM structures, including FSL [11] or FreeSurfer [22], reveals volume loss in deep GM structures in MS patients, particularly the thalamus [23–26]. Although the thalamus was examined most extensively in patients with MS [23], some studies also demonstrated the involvement of other subcortical structures such as the putamen [27]. Recently, measurement of the total lesion load or volume detectable lesions on MRI has become a widely used outcome measure for assessing the efficacy of new therapies in multiple sclerosis [28, 29] (Figs. 6, 7 and 8).

Version 5.0.10 of FSL and Version 7.4.0 of MIPAV software package was used in our study.

Our study included 31 patients diagnosed with RRMS and 31 control subjects of the same age range.

The studied patients group presented variable degrees of clinical disability; this variability was represented by different EDSS scores which ranged from 1 to 6.5, with a mean score of 3.64 and a standard deviation of 1.39.

Each subject in this study underwent a specialized brain imaging protocol with the two main sequences specific for this study being 3D T1W SPGR and 3D T2 FLAIR; both were later used to quantify the volumes of deep grey matter structures and white matter lesions, respectively. This is consistent with the study by Hu et al. [30], stating that 3D MRI sequences are the most commonly used scans for measuring brain volumes and that 3D versions

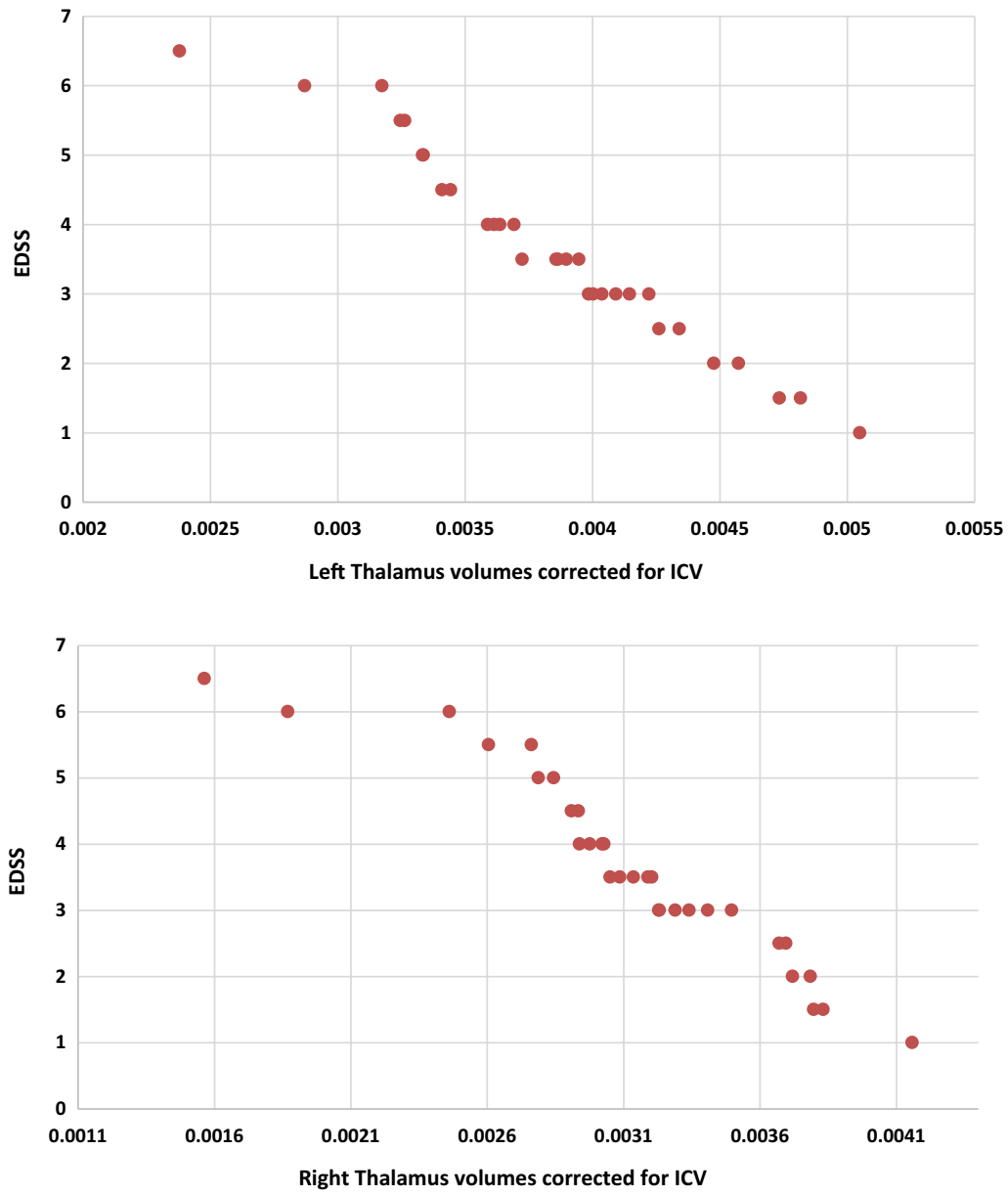
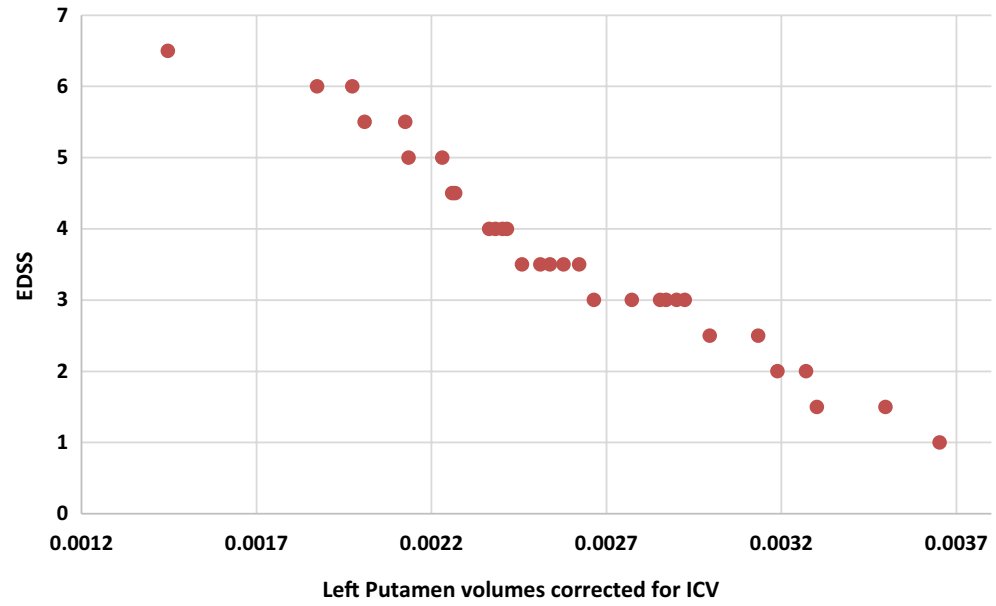


Fig. 1 Correlation between left and right thalamus volumes and EDSS scores

of MRI scans for MS will continue to replace their 2D counterparts, as the 3D scans have a more superior image quality and provide more information.

After calculating the volumes of deep grey matter structures and white matter lesions, these absolute volumes were later converted to relative volumes by correcting for intracranial volume (ICV) of each subject. According to Sanfilipo et al. [31] and Miller et al. [32], this step is crucial as such normalization is particularly important in cross-sectional studies where inter-subject comparisons are performed to adjust raw inter-subject differences in regional brain measurements and reduce the error variance, in contrast with longitudinal studies based on intrasubject comparisons.

The results of our study indicated that the thalamus and putamen in both hemispheres had significantly smaller volumes in RRMS patients compared with age matched controls. Furthermore, the other deep grey matter structures showed no significant volume differences between RRMS patients and controls. Additionally, they showed



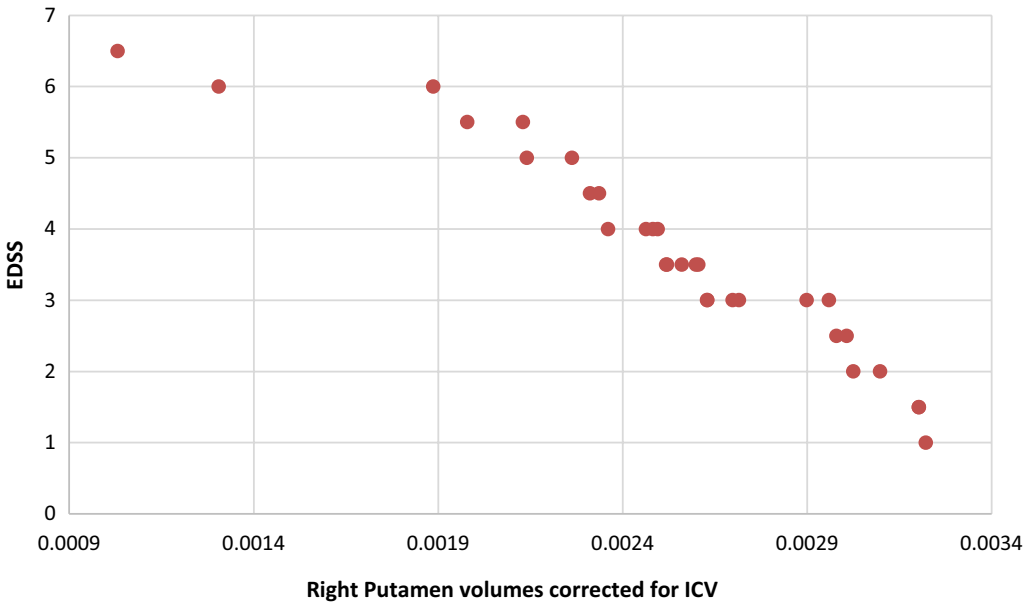


Fig. 2 Correlation between left and right putamen volumes and EDSS scores

that higher EDSS scores were associated with smaller volumes of the thalamus and putamen, and larger volumes of white matter lesions. A significant positive correlation was found between the corrected white matter lesion volumes and EDSS scores, while a significant negative correlation was found between the corrected volumes of the thalamus and putamen, and EDSS scores.

Our work has matched previous studies to a great extent as in Azevedo et al. [33] and Jakimovski et al. [34] which has shown that thalamic volume decreases significantly in MS patients with significant negative correlation with EDSS scores.

Another study by Magon et al.[35] has shown that volumes of the thalamus and the putamen were associated with the EDSS, as they found significant negative correlation between their volumes and the EDSS scores, with the thalamic volume having more significant results.

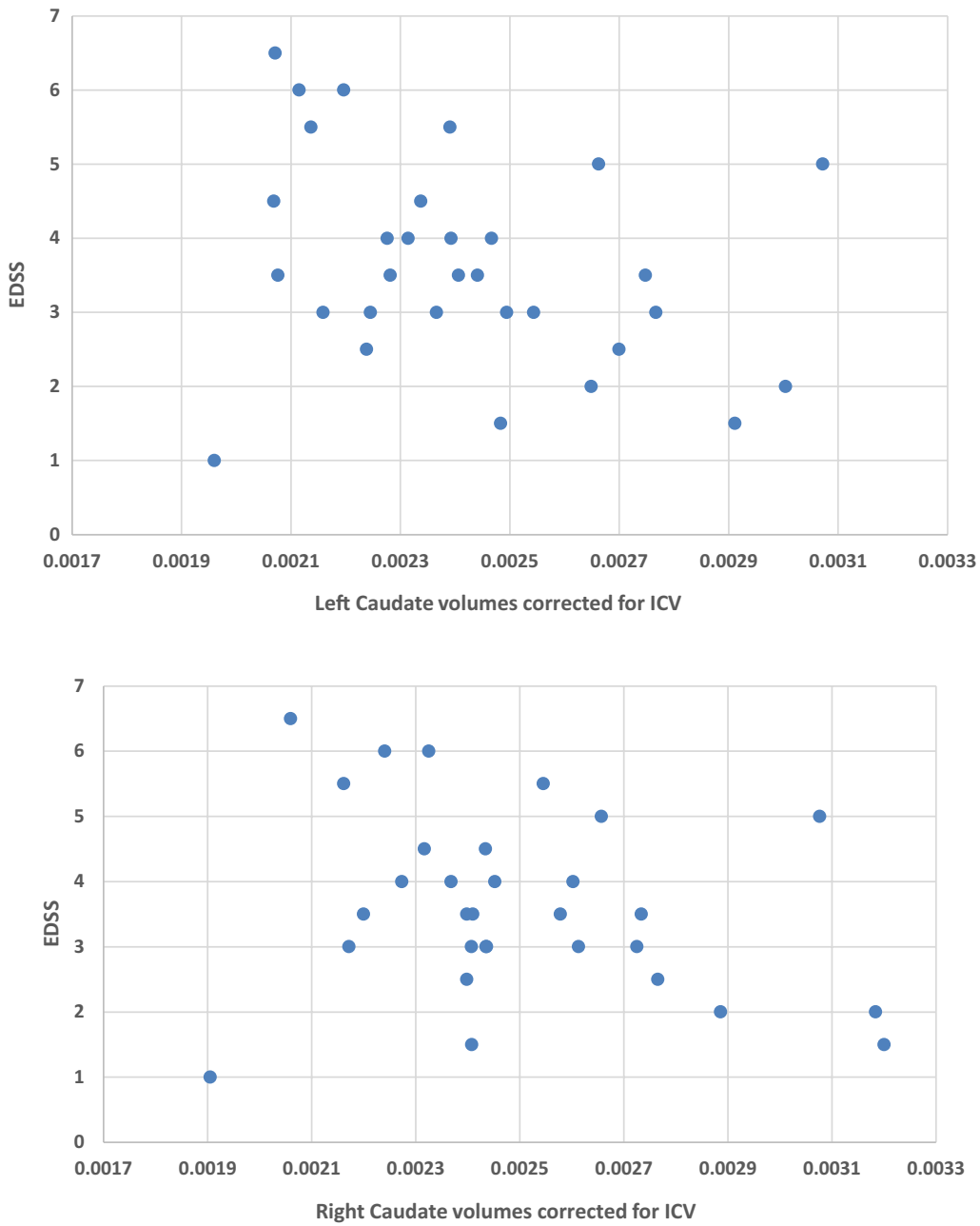


Fig. 3 Correlation between left and right caudate volumes and EDSS scores

While the thalamic atrophy was the main focus of many studies done on RRMS patients, some other studies reported volume loss of the putamen in MS patients; as in the study by Debernard et al. [36] where they reported significant volume reduction in the thalamus as well as the putamen, and they found association between putamen volume loss and performance deficits in executive functions and working memory.

On the other hand, Krämer et al. [37] focused primarily on the putamen volume loss in their study, where they reported early and degressively increasing putamen atrophy in patients with RRMS; they also associated these findings with EDSS scores and cognitive performance which is in agreement with the findings of our study.

In the study by Shiee et al. [38], it was reported that there was significant volume loss of all deep grey matter structures in MS patients (including thalamus, putamen

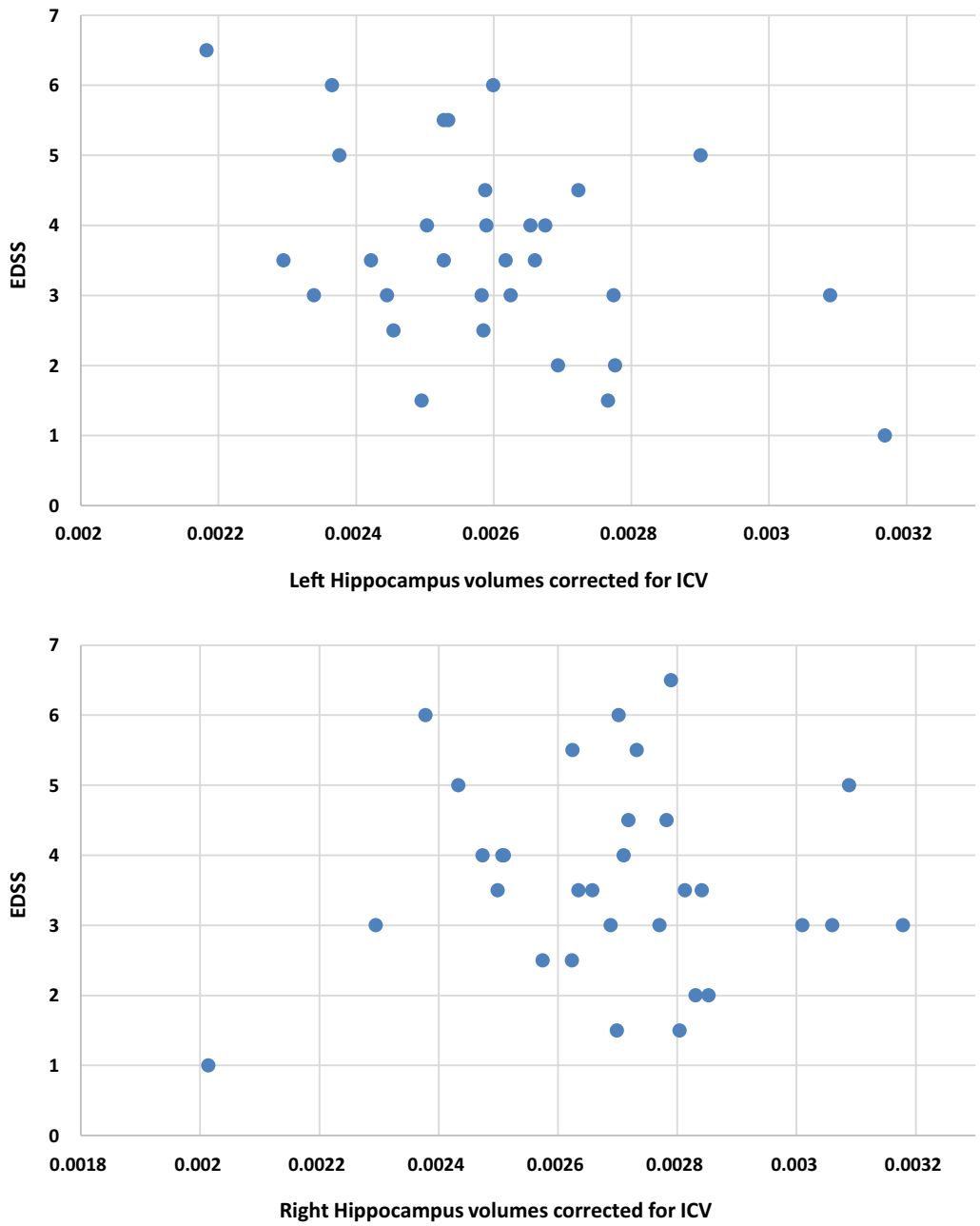


Fig. 4 Correlation between left and right hippocampus volumes and EDSS scores

and caudate), which is partially consistent with our findings where the caudate didn't show significant atrophy. This can be due to differences in sample size and age as our study had a smaller sample and our studied subjects were younger.

A study by Anderson et al. [39] reported a significant hippocampal volume loss in RRMS patients when compared with healthy controls. This is inconsistent with our findings, as we found only a few cases with unilateral hippocampal volume loss in RRMS patients, but on the group level analysis there was no significant difference in hippocampal volume between RRMS and healthy controls. This can be due to differences in demographics between the studies, as our studied sample was a younger age group.

Regarding the white matter lesion volume and its correlation with EDSS scores, a recent study by Nakamura et al. [40] reported a significant positive correlation

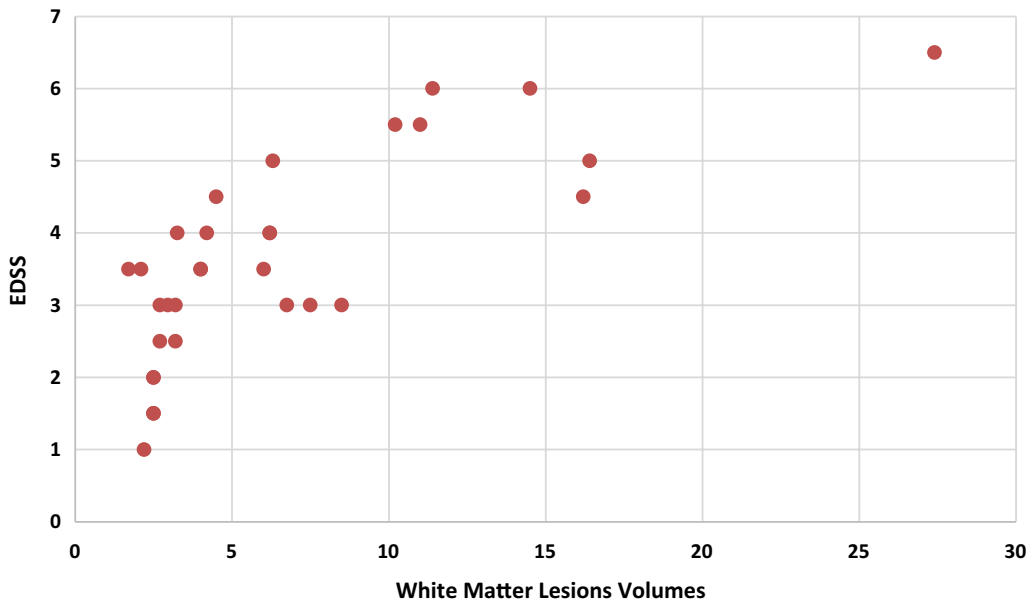


Fig. 5 Correlation between white matter lesions volumes and EDSS scores

between T2W white matter lesion volumes and EDSS scores in MS patients, which is consistent to a great extent with our findings.

This significant positive correlation between white matter lesion volume and EDSS scores in RRMS patients was also reported in other studies by Caramanos et al. [41] as they studied the relationship between clinical disability and cerebral white matter lesion load in patients with MS and they found high positive correlation between white matter lesion volume and EDSS scores specifically in RRMS patients.

Limitation of the study

There are some limitations to our study. Firstly, we used a relatively small sample size, which can produce type I error and can miss subtle differences in volume between the patients and controls. This can be prevented by using a larger sample size. Secondly, we excluded the measurements for cortical grey matter, brain stem, and cerebellar volumes from our study, which could have had an effect on the results of our study. We also did not account for the locations of white matter lesions and its association with disease progression and disability as discussed in previous studies. Another limitation was the lack of a longitudinal study, which could have shown us the dynamic correlation between disease progression, disability, and deep grey matter atrophy which can progress further along the course of the disease; however, this couldn't be done in the current cross-sectional study.

Recommendation

Future studies on this subject can benefit from including other subtypes of MS, as PPMS and SPMS, which can aid specific patterns of brain structure volume loss related to each subtype.

We recommend using higher field MR scanner, as 3T or 7T, in such sophisticated studies to have higher resolution images which can help in better visualization of lesions and more robust segmentation and quantification results which in turn will lead to better detection of very subtle changes in these patients.

Conclusions

Automated segmentation and quantification tools have a great role in the assessment of brain structural changes in RRMS patients, and that it became essential to integrate these tools in the daily medical practice for the great value they add to the current evaluation measures. MRI and volumetric measurements of the deep grey matter structures should be included as routine modality when evaluating patients with MS.

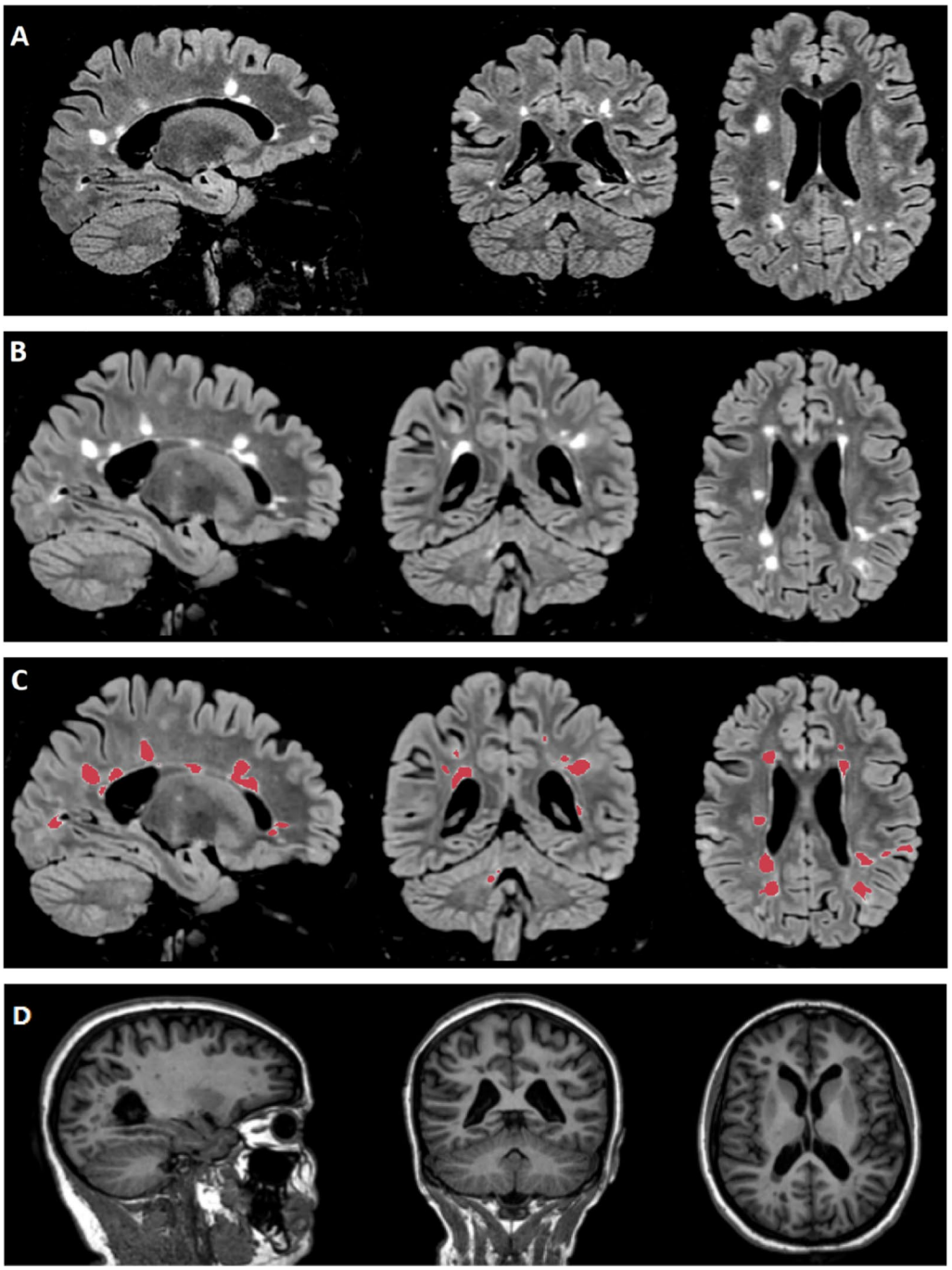


Fig. 6 A female patient aged 23 years, known to have RRMS with EDSS score of 5.5. White matter lesions segmentation: T2 FLAIR images in sagittal, coronal, and axial planes; **a** raw unprocessed image showing white matter hyperintense lesions located at the periventricular and deep white matter, **b** T2 FLAIR image after registration to MNI template and **c** processed T2 FLAIR image with segmented white matter lesions. Deep grey matter structures segmentation: T1W images in sagittal, coronal, and axial planes; **d** raw unprocessed T1W images, **e** T1W images after registration to MNI template, and **f** and **g** T1W images with coloured segmented grey matter structures with thalamus in orange, caudate in red, putamen in green, and hippocampus in blue. Grey matter structures volumes after correction for ICV: Left and right thalamus: 0.00326 and 0.00276 cm^3, left and right caudate: 0.00239 and 0.00254 cm^3, left and right putamen: 0.00213 and 0.00213 cm^3, left and right hippocampus: 0.00253 and 0.00262 cm^3. White matter lesions volume: 10.2 cm^3. We found that the patient had a significant decrease in the volumes of the thalamus and putamen bilaterally with white matter lesions volume of 10.2 cm^3 and EDSS score of 5.5

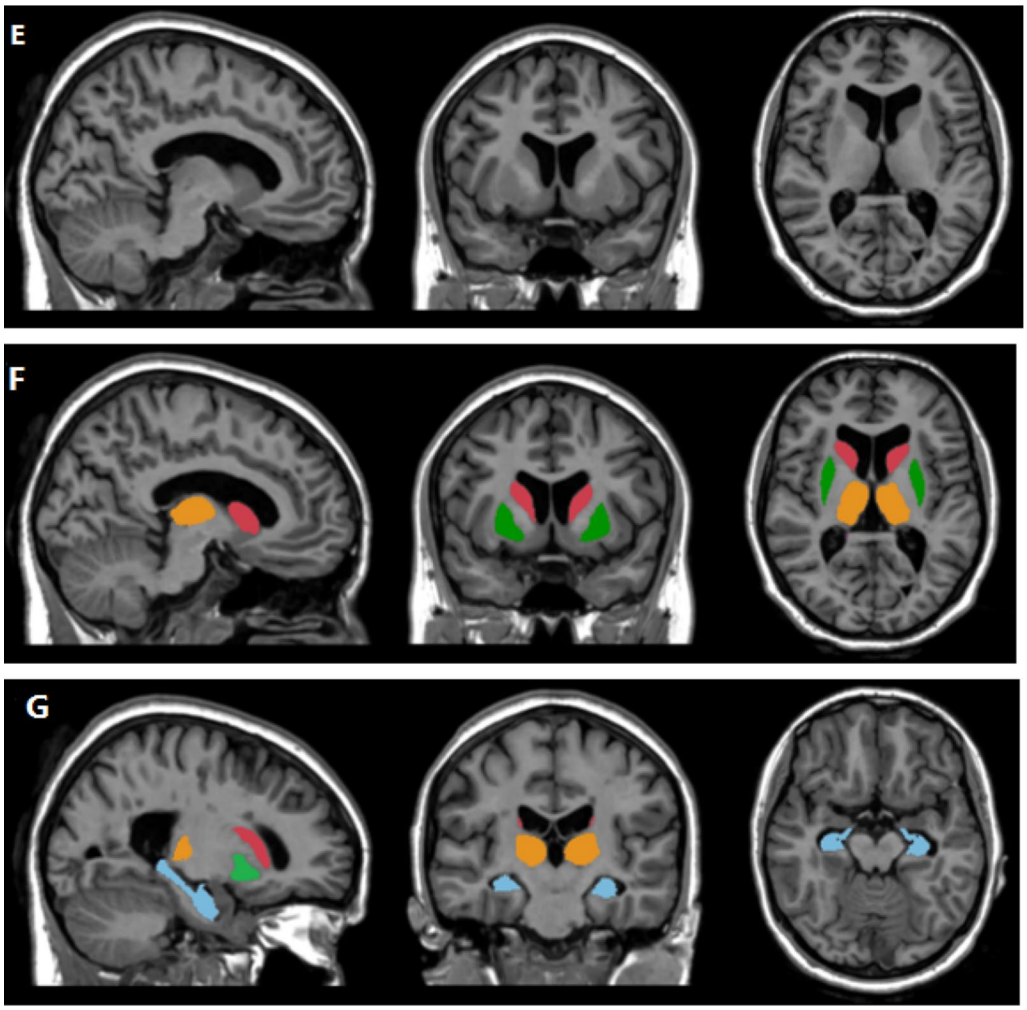


Fig. 6 continued

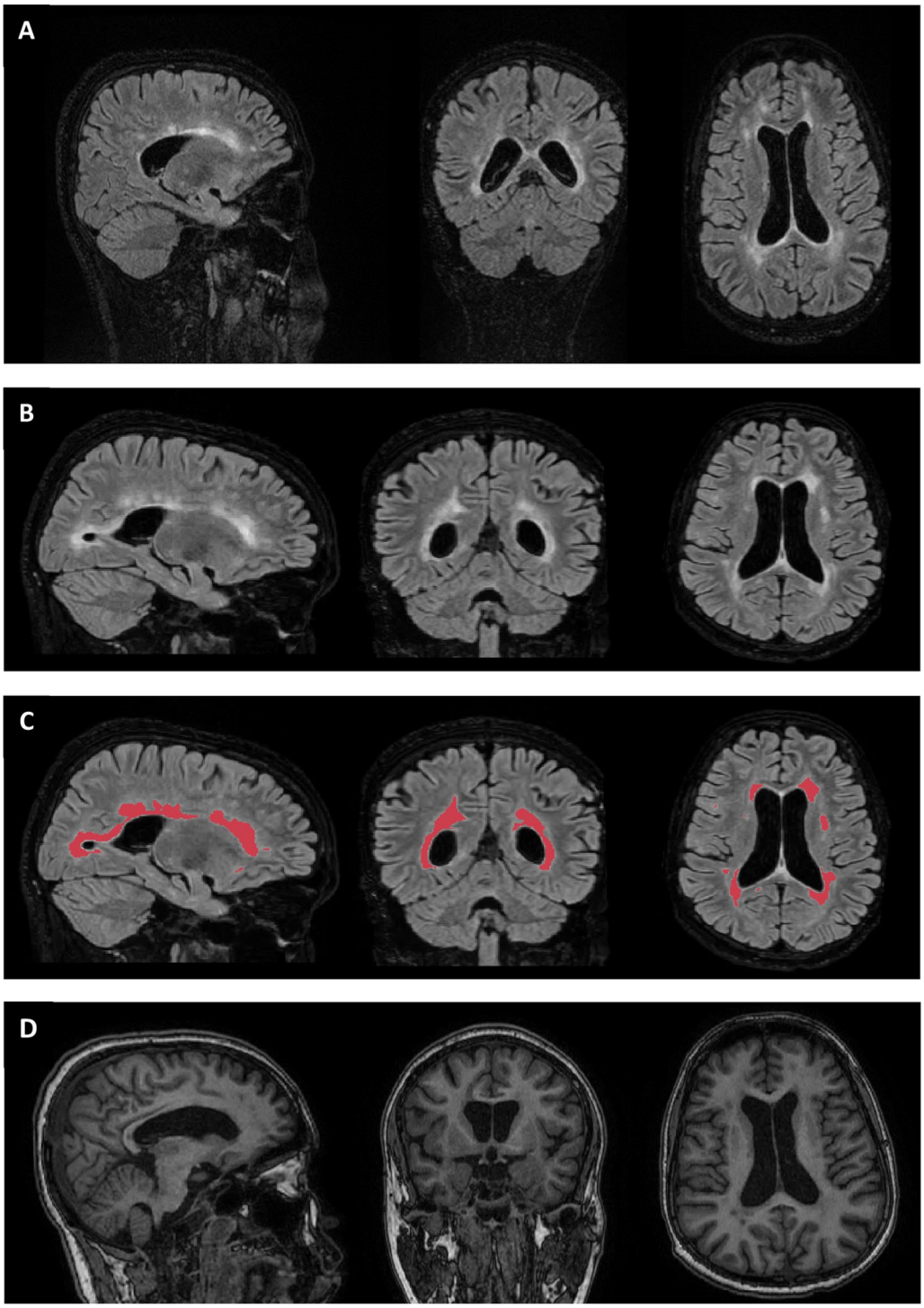


Fig. 7 A male patient aged 27 years, known to have RRMS with EDSS score of 3.5. White matter lesions segmentation: T2 FLAIR images in sagittal, coronal, and axial planes; **a** raw unprocessed image showing white matter hyperintense lesions located at the periventricular and white matter, **b** T2 FLAIR image after registration to MNI template and **c** processed T2 FLAIR image with segmented white matter lesions. Deep grey matter structures segmentation: T1W images in sagittal, coronal and axial planes; **d** raw unprocessed T1W images, **e** T1W images after registration to MNI template, and **f** and **g** T1W images with coloured segmented grey matter structures with thalamus in orange, caudate in red, putamen in green, and hippocampus in blue. Grey matter structures volumes after correction for ICV: Left and right thalamus: 0.00395 and 0.00321 cm^3, left and right caudate: 0.00275 and 0.00273 cm^3, left and right putamen: 0.00262 and 0.00261 cm^3, left and right hippocampus: 0.00229 and 0.00263 cm^3. White matter lesions volume: 1.7 cm^3. We found that the patient had a significant decrease in the volumes of the putamen bilaterally, right thalamus, and left hippocampus, and he had white matter lesions volume of 1.7 cm^3 and EDSS score of 3.5

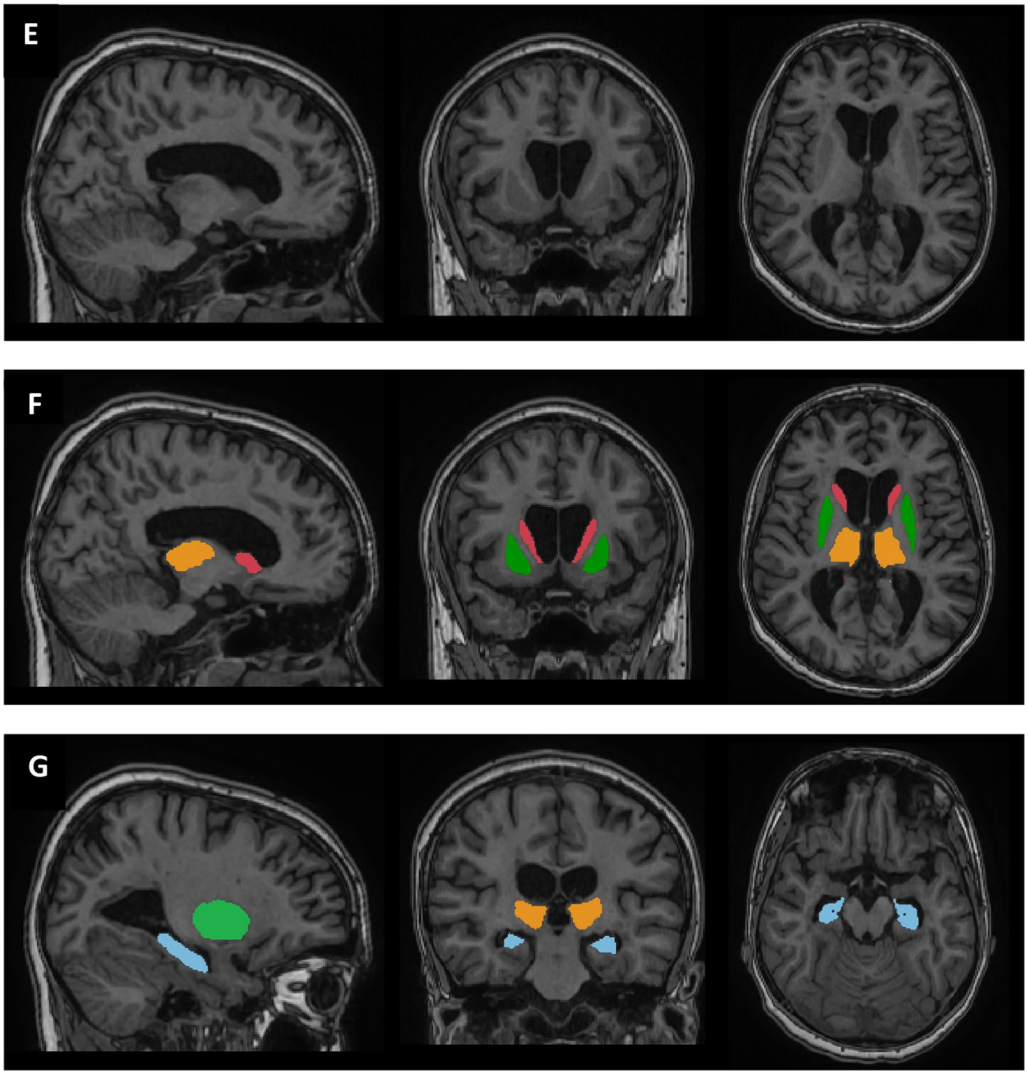


Fig. 7 continued

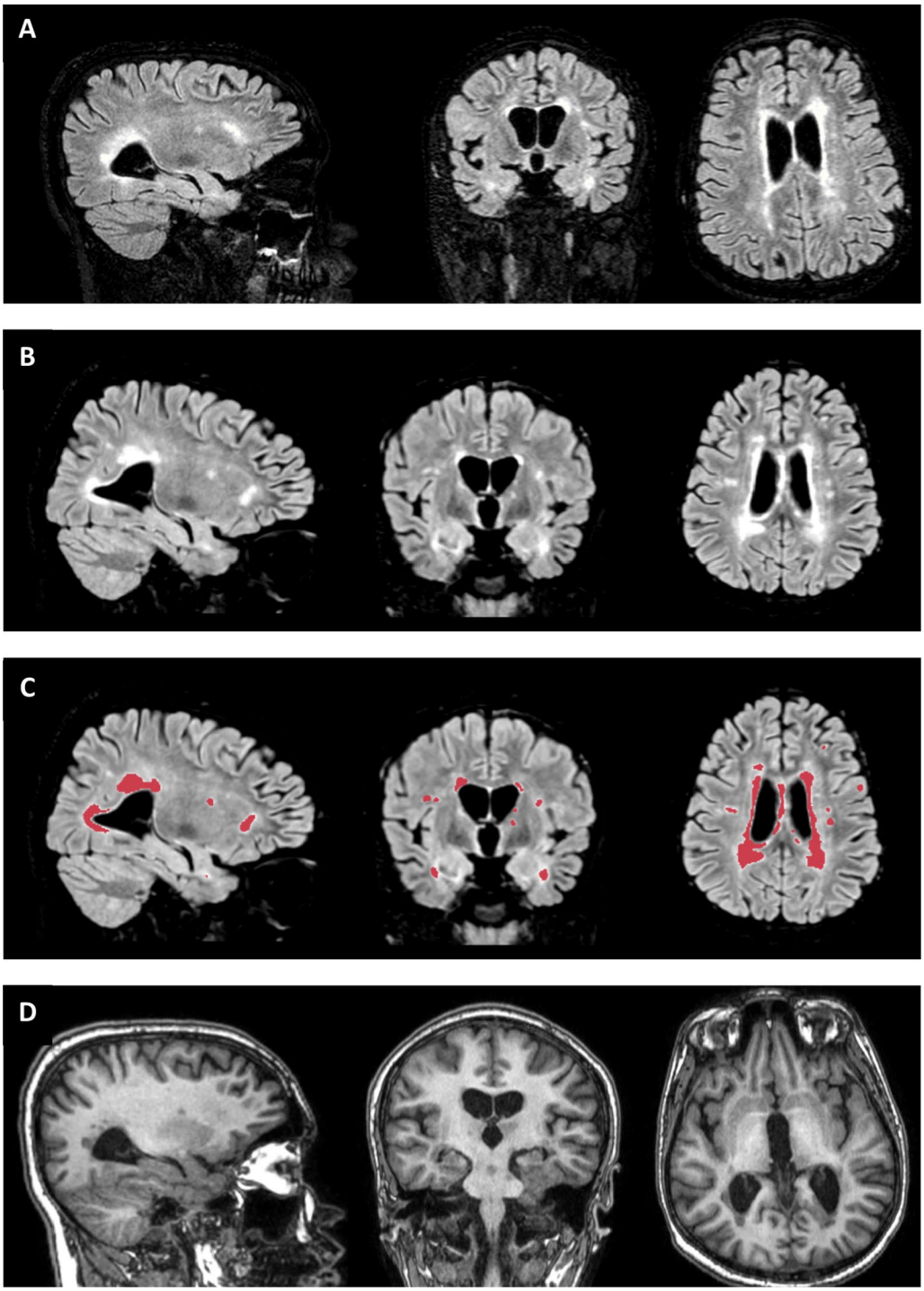


Fig. 8 A female patient aged 24 years, known to have RRMS with EDSS score of 3. White matter lesions segmentation: T2 FLAIR images in sagittal, coronal, and axial planes; **a** raw unprocessed image showing white matter hyperintense lesions located mainly at the periventricular white matter with a few small juxtacortical lesions, **b** T2 FLAIR image after registration to MNI template and **c** processed T2 FLAIR image with segmented white matter lesions. Deep grey matter structures segmentation: T1W images in sagittal, coronal, and axial planes; **d** raw unprocessed T1W images, **e** T1W images after registration to MNI template, and **f** and **g** T1W images with coloured segmented grey matter structures with thalamus in orange, caudate in red, putamen in green, and hippocampus in blue. Grey matter structures volumes after correction for ICV: Left and right thalamus: 0.00404 and 0.00329 cm^3, left and right caudate: 0.00277 and 0.00272 cm^3, left and right putamen: 0.00285 and 0.00270 cm^3, left and right hippocampus: 0.00272 and 0.00277 cm^3. White matter lesions volume: 6.75 cm^3. We found that the patient had a significant decrease in the volumes of the right thalamus, and the right putamen, and she had white matter lesions volume of 6.75 cm^3 and EDSS score of 3

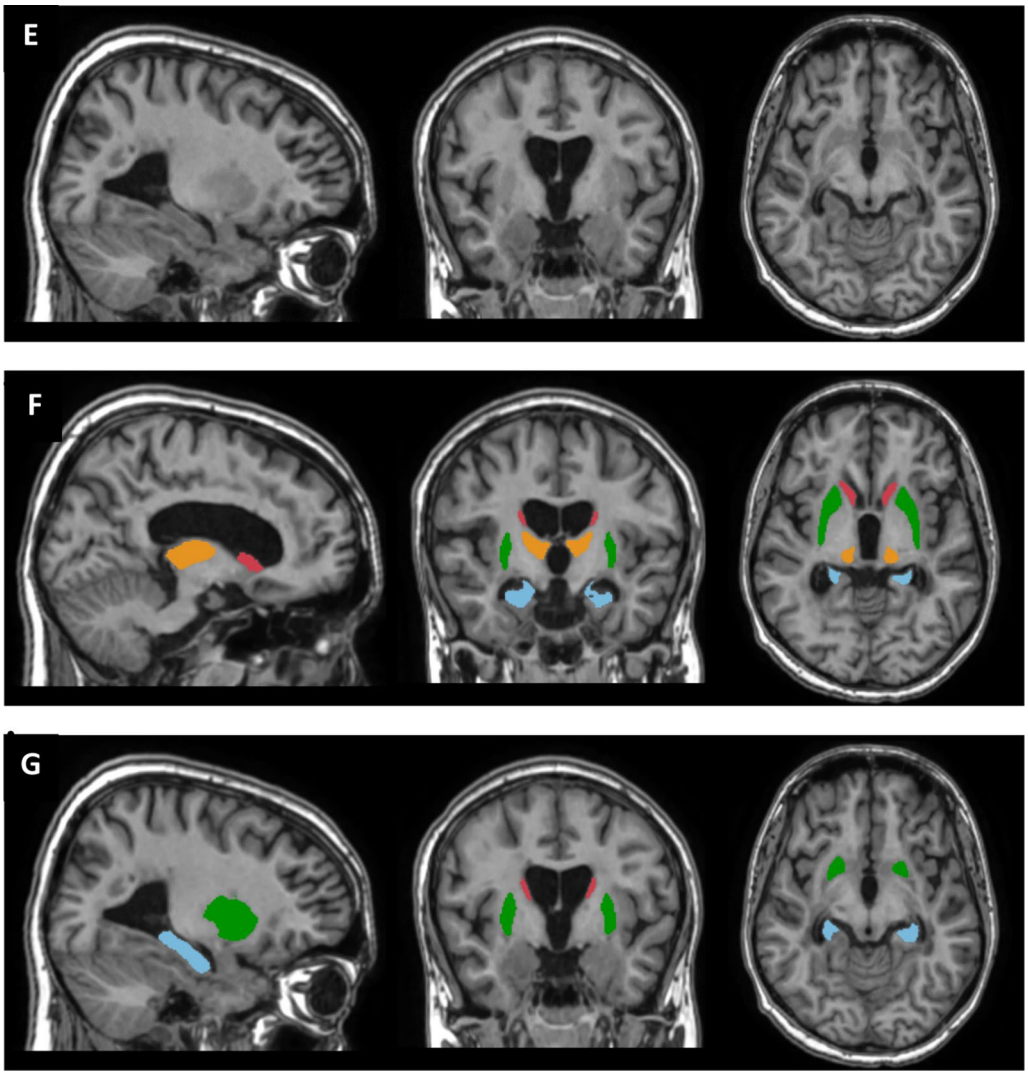


Fig. 8 continued

Abbreviations
BVL: Brain volume loss; EDSS: Expanded disability status scale; MS: Multiple sclerosis; RRMS: Relapsing remission relapse; SPGR: Sagittal 3D T1-weighted spoiled gradient; WM: White matter; DGM: Deep grey matter; FLAIR: Fluid attenuation inversion recovery; ICV: Intracranial volume; MNI: The Montreal Neuroimaging Institute template dataset; CMA: Center for Morphometric Analysis; FSL: FMRIB software library; FLIRT: FSL linear image registration tool; MIPAV: Medical image processing, analysis, and visualization; HC: Healthy control.

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Authors' contributions
MF suggested the research idea, ensured the original figures and data in the work, minimized the obstacles to the team of work, correlated the study concept and design, and had the major role in analysis, MH supervised the study with significant contribution to design the methodology, manuscript revision, and preparation. MK correlated the clinical data of patient and matched it with the findings, drafted, and revised the work. RD collected data in all stages of manuscript and performed data analysis. All authors read and approved the final manuscript for submission.

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Availability of data and materials
The author's confirm that all data supporting the finding of the study are available within the article and the raw data and data supporting the findings were generated and available at the corresponding author on request.

Declarations

Ethics approval and consent to participate
Informed written consents were taken from the patients and healthy volunteers, the study was approved by ethical committee of Tanta university hospital, faculty of medicine (31544/05/17).

Consent for publication
All participants included in the research gave written consent to publish the data included in the study. Authors accepted to publish the paper.

Competing interests
The authors declare that they have no competing of interests.

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