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Brain magnetic resonance imaging surface-based analysis and cortical thickness measurement in relapsing remission multiple sclerosis

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Abstract

Background: Damage occurs in the brain tissue in MS which appears normal on standard conventional imaging (normal appearing brain tissue). This slow, evolving damage can be monitored by nonconventional advanced MR imaging techniques. New techniques for the measurement of cortical thickness have been validated against histological analysis and manual measurements. The aim of our study was to study the role of MRI surface-based analysis and cortical thickness measurement in the evaluation of patients with Relapsing Remitting Multiple Sclerosis and to detect if there is localized rather than generalized cortical atrophy in Multiple Sclerosis patients and correlating these findings with clinical data.

Results: 30 patients and 30 healthy control were included in this study and they were subjected to cortical thickness analysis using MRI. The patients in our study showed decreased thickness of the precentral, paracentral, postcentral, posterior cingulate cortices and mean cortical thickness in both hemispheres when compared with the normal control group. Statistical analysis was significant (P value < 0.05) for the precentral, paracentral, postcentral, posterior cingulate cortices and mean cortical thickness in both hemispheres. On the other hand, statistical analysis was not significant (P value > 0.05) for other cortices. There was a significant negative correlation between the precentral, paracentral, postcentral, posterior cingulate cortices and mean cortical thickness in both hemispheres and EDSS scores with correlation coefficients ranging from -0.9878 to -0.7977 .

Conclusions: MRI and post-processing segmentation analysis for cortical thickness is non-invasive imaging techniques that can increase the level of diagnostic confidence in diagnosis of MS patients and should be included as routine modality when evaluating patients with MS.

Keywords: Multiple sclerosis, MRI volumetry in RRMS, Cortical thickness, Cortical atrophy

Background

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system characterized by lesion formation and atrophy [1]. Although traditional thinking has considered focal areas of white

matter demyelination as the key feature of MS rather than cortical gray matter (GM) atrophy, recent studies have confirmed greater tissue loss in the cortical GM compartment, and early pathologic studies had reported cortical demyelination in MS patients [1–4].

This focus on white matter demyelination rather than cortical pathology was initially compounded with the advent of Magnetic Resonance Imaging (MRI): conventional MRI techniques for imaging MS identify a majority

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of focal white matter lesions but are very insensitive for the detection of cortical atrophy [5].

In association with cortical demyelination that clearly occurs in MS, there is also evidence of damage to the neurons themselves: multiple studies show evidence of neuronal atrophy, apoptosis, decreased neuronal densities, and reduced synaptic and glial densities [6–8], while gray matter atrophy in MS is a global and widespread phenomenon, it appears that the location of atrophy (i.e., what specific brain region is affected) may be as important as global cortical atrophic changes [9].

It is now clear that damage also occurs in the brain tissue which appears normal on standard conventional imaging (normal appearing brain tissue). This slow, evolving damage can be monitored by nonconventional advanced MR imaging techniques [9].

New techniques for the measurement of cortical thickness have been validated against histological analysis [10] and manual measurements [11].

Isotropic, high-resolution T1 weighted (T1-W) 3D volumetric acquisitions are best able to detect the small changes which occur over time. This is usually measured as changes in cortical thickness measurements [12].

These new techniques enable mapping the affected cortical brain regions to assess whether the cortical involvement is localized rather than diffuse, also the extent of atrophic changes in the affected regions. These techniques include advanced post-processing pipelines that pass through the steps of image registration, cortical segmentation, cortical thickness measurements and statistical analysis; all these steps can be done by highly advanced software packages like FreeSurfer [13].

The aim of our study was to study the role of MRI surface-based analysis and cortical thickness measurement in the evaluation of patients with Relapsing Remitting Multiple Sclerosis and to detect if there is localized rather than generalized cortical atrophy in Multiple Sclerosis patients and correlating these findings with different grades of disability based on EDSS scores.

Methods

Study design and population

This prospective study was carried on 30 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 November 2017 to February or further MRI assessment. 30 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 contraindication for MRI scan, for example: Patients who have a cardiac pacemaker, patients who have a metallic prosthesis or patients with bad general condition. Abnormal morphology of the brain as encephalomalacia, gliosis, polymicrogyria, etc.

Ethics committee approved and informed consent were obtained for all patients or their guardians'. Privacy and confidentiality of all patients data were guaranteed, and 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 including:
 - Name, age, sex and marital status.
 - Symptoms and signs: including manifestations of cognitive impairment and behavioral changes.

The Expanded Disability Status Scale (EDSS) was done for all patients. 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 [14].

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 [15].

2. Neuroimaging data acquisition:

Brain MRI was performed on a 1.5 Tesla GE closed-configuration whole body scanner using a standard quadrature head coil.

The patients were positioned as follows:

- Patient Entry: Head First
- Patient Position: Supine
- Coil Configuration: Head coil

All patients were subjected to the following protocol:

(I) MRI scanning

Sagittal 3D T1 weighted spoiled gradient (SPGR) utilizing the following parameters: A repetition time (TR) of 7.2 ms, an echo time (TE) of 120 ms, a slice thickness of 1.2 mm, FOV = 256 × 256 mm (Table 1).

(II) Image processing and analysis

Table 1 Imaging parameters used for acquiring 3D T1W sequence

| Imaging parameters | 3D T1W SPGR |
|--|--------------|
| Plane | Sagittal |
| Mode | 3D |
| Pulse sequence | SPGR |
| Prep. time | 500 ms |
| Inversion time | – |
| TE | Minimum full |
| TR | 7.2 ms |
| FOV | 256 × 256 mm |
| Phase FOV | 1.0 |
| Slice thickness | 1.2 mm |
| Number of slices | 160 |
| Slice spacing | Zero |
| Matrix | 192 × 192 |
| Flip angle | 10° |
| Frequency | 16 kHz |
| Freq DIR | S/I |
| NEX | 1.0 |
| Shim | Auto |
| Phased array uniformity enhancement (PURE) | On |
| Surface coil intensity correction (SCIC) | Off |

Cortical thickness analysis

Cortical reconstruction and segmentation were performed with the FreeSurfer image analysis suite, which is documented and freely available for download online.

The processing includes removal of non-brain tissue using a hybrid watershed/surface deformation procedure, automated Talairach transformation, intensity normalization, tessellation of the gray matter white matter boundary, automated topology correction, and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class.

Once the cortical models are complete, a number of deformable procedures were performed for further data processing and analysis including surface inflation, registration to a spherical atlas which is based on individual cortical folding patterns to match cortical geometry across subjects, parcellation of the cerebral cortex into units with respect to gyral and sulcal structure and creation of a variety of surface-based data including maps of curvature and sulcal depth.

Measurement of the cortical thickness is calculated after identification of the cortical surfaces into cortex, outside of cortex (pial surface, cortical CSF, and background) and inside of cortex (white matter and deep gray matter), and then paths running between

the inside and outside boundaries identified and their lengths measured.

This method uses both intensity and continuity information from the entire three-dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface [16].

The maps are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. The maps produced are not restricted to the voxel resolution of the original data thus can detect submillimeter differences between groups.

(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 analyzed using IBM SPSS software package version 20.0.
- Quantitative data were described using range (minimum and maximum), mean and standard deviation.
- Comparison of cortical thickness quantitative findings with normal values was done using one sample z-test.
- Pearson correlation coefficient was calculated to test the correlation between the cortical thickness findings 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 .

(V) Surface-based analyses

Vertex-based General Linear Model (GLM) analysis: The group differences of cortical thickness were calculated using GLM analysis. The whole brain vertex-based analysis is a point-by-point group comparison of thickness across the cortical surface, without any priori hypothesis, starting with the average images of each group. Age and disease duration were included as covariates of no interest in GLM analysis. Then, the statistically significant results are represented on a cortical reconstruction surface and inflated brain surface templates. Significance was set to a P value of < 0.05 [17].

Results

I. Demographic data

The study included 30 patients diagnosed with RRMS, and the age ranged between 20–35 years old with mean age of 27.54 years old. The age distribution of the studied group was 40% from 20 to 25 years old, 26.6% from 26 to 30 years old and 33.3% from 31 to 35 years old. 26.6% of the patients were male patients and 73.3% of them were female.

The distribution of EDSS scores of the studied group was 23.3% from 1 to 2.5, 53.3% from 3 to 4.5 and 23.3% from 5 to 6.5.

II. Mean cortical thickness difference of both hemispheres

The mean cortical thickness values on both sides showed a significant decrease in the RRMS group compared to the control group with a Z-score of -2.01 and a P value of 0.04 for the left mean cortical thickness and a Z-score of -2.16 and a P value of 0.03 for the right mean cortical thickness. The mean cortical thickness of the left hemisphere for the RRMS group was 2.258 mm with a standard deviation of 0.087 mm while the control group had a mean cortical thickness of 2.488 mm with a standard deviation of 0.115 mm. As for the mean cortical thickness of the right hemisphere, the RRMS group thickness was 2.249 mm with a standard deviation of 0.087 mm and the control group had a mean cortical thickness of 2.476 mm with a standard deviation of 0.105 mm (Table 2).

III. Cortical thickness results of the left frontal Lobe

There was significant decrease in the cortical thickness in the RRMS group compared to the control group in the left precentral cortex and the left paracentral cortex. The Z-score for the left precentral cortex was -3.46 (P value <0.05) with a mean thickness of 2.0875 mm and a standard deviation of 0.127 mm for the RRMS group, while the mean thickness for the control group was 2.564 mm with a standard deviation of 0.137 mm. The Z-score

for the left paracentral Cortex was -2.46 (P value <0.05) with a mean thickness of 2.0246 mm and a standard deviation of 0.131 mm for the RRMS group, while the mean thickness was 2.375 mm with a standard deviation of 0.142 mm for the control group (Table 3).

IV. Cortical thickness results of the left parietal lobe

There was significant decrease in the cortical thickness in the RRMS group compared to the control group in the left postcentral cortex and the left posterior cingulate cortex. The Z-score for the left postcentral cortex was -3.69 (P value <0.05) with a mean thickness of 1.5931 mm and a standard deviation of 0.114 mm for the RRMS group, while the mean thickness for the control group was 2.0696 mm with a standard deviation of 0.129 mm. The Z-score for the left posterior cingulate cortex was -2.89 (P value <0.05) with a mean thickness of 1.9651 mm and a standard deviation of 0.197 mm for the RRMS group, while the mean thickness was 2.4416 mm with a standard deviation of 0.168 mm for the control group (Table 3).

XXII. Cortical thickness results of the left temporal lobe

There was no significant difference in the cortical thickness of the left temporal lobe between the RRMS and control groups (Table 4).

VI. Cortical thickness results of the left occipital lobe

There was no significant difference in the cortical thickness of the left occipital lobe between the RRMS and control groups (Table 4).

VII. Cortical thickness results of the right frontal lobe

There was significant decrease in the cortical thickness in the RRMS group compared to the control group in the right precentral cortex and the right paracentral cortex. The Z-score for the right precentral cortex was -3.85 (P value <0.05) with a mean thickness of 2.0651 mm and a standard deviation of 0.123 mm for the RRMS group, while the mean thickness for the control group was 2.5216 mm with a standard deviation of 0.119 mm. The Z-score for the right paracentral cortex was -2.23 (P value <0.05) with a mean thickness of 2.0618 mm and a standard deviation of 0.141 mm for the RRMS group, while the mean thickness was 2.3922 mm with a standard deviation of 0.148 mm for the control group (Table 5).

VIII. Cortical thickness results of the right parietal lobe

There was significant decrease in the cortical thickness in the RRMS group compared to the control group in the right postcentral cortex and the right posterior cingulate cortex. The Z-score for the right postcentral cortex was -3.31 (P value <0.05) with a mean thickness of 1.5947 mm and a standard deviation of 0.111 mm for

Table 2 Quantitative results of the mean cortical thickness in mm of the left and right hemisphere for patients and control groups, Z-scores and P values

| Mean cortical thickness | Cases (n = 30) | Control (n = 30) | Z-scores | P values |
|-------------------------|-------------------|-------------------|----------|----------|
| <i>Left</i> | | | | |
| Min.–Max | 2.095–2.435 | 2.164–2.636 | -2.01 | 0.04 |
| Mean \pm SD | 2.258 ± 0.087 | 2.488 ± 0.115 | | |
| <i>Right</i> | | | | |
| Min.–Max | 2.077–2.431 | 2.205–2.663 | -2.16 | 0.03 |
| Mean \pm SD | 2.249 ± 0.087 | 2.476 ± 0.105 | | |

Table 3 Quantitative results of the cortical thickness in mm of the left frontal and parietal lobe areas in mm for patients and control groups, Z-scores and P values

| Cortex name | Patient (mean ± SD) | Control (mean ± SD) | Z-score | P value |
|---|---------------------|---------------------|---------|---------|
| <i>Left frontal lobe cortical thickness (mm)</i> | | | | |
| Frontal pole | 2.4196 ± 0.230 | 2.72 ± 0.293 | − 1.02 | 0.3 |
| Superior frontal | 2.5087 ± 0.109 | 2.7366 ± 0.126 | − 1.81 | 0.06 |
| Middle frontal | 2.2394 ± 0.108 | 2.4898 ± 0.149 | − 1.67 | 0.09 |
| Lateral orbito– frontal | 2.3558 ± 0.163 | 2.6062 ± 0.136 | − 1.84 | 0.06 |
| Medial orbito-frontal | 2.2759 ± 0.164 | 2.5134 ± 0.127 | − 1.86 | 0.06 |
| Pars opercularis | 2.3633 ± 0.120 | 2.6437 ± 0.148 | − 1.88 | 0.05 |
| Pars triangularis | 2.2096 ± 0.123 | 2.49 ± 0.193 | − 1.45 | 0.14 |
| Pars orbitalis | 2.3451 ± 0.165 | 2.6255 ± 0.189 | − 1.48 | 0.13 |
| Precentral | 2.0875 ± 0.127 | 2.564 ± 0.137 | − 3.46 | 0.0005 |
| Anterior cingulate | 2.516 ± 0.27 | 2.7664 ± 0.23 | − 1.09 | 0.27 |
| Paracentral cortex | 2.0246 ± 0.131 | 2.375 ± 0.142 | − 2.46 | 0.01 |
| <i>Left parietal lobe cortical thickness (mm)</i> | | | | |
| Postcentral | 1.5931 ± 0.114 | 2.0696 ± 0.129 | − 3.69 | 0.0002 |
| Superior parietal | 1.959 ± 0.102 | 2.2094 ± 0.144 | − 1.73 | 0.08 |
| Inferior parietal | 2.2176 ± 0.134 | 2.468 ± 0.132 | − 1.89 | 0.05 |
| Supramarginal | 2.3119 ± 0.115 | 2.5623 ± 0.137 | − 1.82 | 0.06 |
| Precuneus | 2.1387 ± 0.124 | 2.3891 ± 0.136 | − 1.84 | 0.06 |
| Posterior cingulate | 1.9651 ± 0.197 | 2.4416 ± 0.168 | − 2.89 | 0.003 |

Table 4 Quantitative results of the cortical thickness in mm of the left temporal and occipital lobe areas in mm for patients and control groups, Z-scores and P values

| Cortex name | Patient (mean ± SD) | Control (mean ± SD) | Z-score | P value |
|--|---------------------|---------------------|---------|---------|
| <i>Left temporal lobe cortical thickness (mm)</i> | | | | |
| Temporal pole | 3.1484 ± 0.377 | 3.4488 ± 0.376 | − 0.79 | 0.42 |
| Superior temporal | 2.5372 ± 0.145 | 2.7876 ± 0.162 | − 1.54 | 0.12 |
| Middle temporal | 2.5823 ± 0.144 | 2.8327 ± 0.149 | − 1.67 | 0.09 |
| Inferior temporal | 2.4443 ± 0.150 | 2.7347 ± 0.181 | − 1.6 | 0.1 |
| Transverse temporal | 2.0892 ± 0.275 | 2.3896 ± 0.242 | − 1.23 | 0.21 |
| Entorhinal cortex | 2.9532 ± 0.699 | 3.2036 ± 0.351 | − 0.71 | 0.47 |
| Para-hippocampal | 2.4818 ± 0.576 | 2.7322 ± 0.308 | − 0.81 | 0.41 |
| Fusiform | 2.4276 ± 0.135 | 2.678 ± 0.155 | − 1.61 | 0.1 |
| Insula | 2.7205 ± 0.176 | 3.0209 ± 0.158 | − 1.89 | 0.05 |
| <i>Left occipital lobe cortical thickness (mm)</i> | | | | |
| Lateral occipital | 1.9043 ± 0.085 | 2.1547 ± 0.166 | − 1.5 | 0.13 |
| Cuneus | 1.6827 ± 0.134 | 1.9331 ± 0.139 | − 1.8 | 0.07 |
| Lingual cortex | 1.8263 ± 0.120 | 2.0767 ± 0.149 | − 1.67 | 0.09 |
| Peri-calcarine cortex | 1.4139 ± 0.195 | 1.6943 ± 0.163 | − 1.72 | 0.08 |

the RRMS group, while the mean thickness for the control group was 2.0513 mm with a standard deviation of 0.138 mm. The Z-score for the right posterior cingulate cortex was − 3.29 (P value < 0.05) with a mean thickness of 1.994 mm and a standard deviation of 0.168 mm

for the RRMS group, while the mean thickness was 2.4505 mm with a standard deviation of 0.159 mm for the control group (Table 5).

IX. Cortical thickness results of the right temporal lobe

Table 5 Quantitative results of the cortical thickness in mm of the right frontal and parietal lobe areas in mm for patients and control groups, Z-scores and P values

| Cortex name | Patient (mean ± SD) | Control (mean ± SD) | Z-Score | P value |
|--|---------------------|---------------------|---------|---------|
| <i>Right frontal lobe cortical thickness (mm)</i> | | | | |
| Frontal pole | 2.4679 ± 0.308 | 2.7179 ± 0.282 | -0.88 | 0.37 |
| Superior frontal | 2.478 ± 0.120 | 2.7084 ± 0.119 | -1.93 | 0.05 |
| Middle frontal | 2.2359 ± 0.11 | 2.4663 ± 0.137 | -1.72 | 0.08 |
| Lateral orbito-frontal | 2.3725 ± 0.169 | 2.6029 ± 0.153 | -1.51 | 0.13 |
| Medial orbito-frontal | 2.2408 ± 0.153 | 2.4712 ± 0.169 | -1.36 | 0.17 |
| Pars opercularis | 2.3679 ± 0.110 | 2.5983 ± 0.163 | -1.41 | 0.15 |
| Pars triangularis | 2.2621 ± 0.129 | 2.4925 ± 0.188 | -1.22 | 0.21 |
| Pars orbitalis | 2.4106 ± 0.227 | 2.641 ± 0.165 | -1.4 | 0.16 |
| Precentral | 2.0651 ± 0.123 | 2.5216 ± 0.119 | -3.85 | 0.0001 |
| Anterior cingulate | 2.4617 ± 0.235 | 2.7421 ± 0.201 | -1.38 | 0.16 |
| Paracentral cortex | 2.0618 ± 0.141 | 2.3922 ± 0.148 | -2.23 | 0.02 |
| <i>Right parietal lobe cortical thickness (mm)</i> | | | | |
| Postcentral | 1.5947 ± 0.111 | 2.0513 ± 0.138 | -3.31 | 0.0009 |
| Superior parietal | 1.9488 ± 0.111 | 2.1792 ± 0.139 | -1.65 | 0.09 |
| Inferior parietal | 2.2251 ± 0.122 | 2.4555 ± 0.141 | -1.63 | 0.1 |
| Supramarginal | 2.2555 ± 0.140 | 2.5055 ± 0.146 | -1.71 | 0.08 |
| Precuneus | 2.1604 ± 0.107 | 2.3908 ± 0.121 | -1.9 | 0.05 |
| Posterior cingulate | 1.994 ± 0.168 | 2.4505 ± 0.159 | -3.29 | 0.0009 |

Table 6 Quantitative results of the cortical thickness in mm of the right temporal and occipital lobe areas in mm for patients and control groups, Z-scores and P values

| Cortex name | Patient (mean ± SD) | Control (mean ± SD) | Z-score | P value |
|---|---------------------|---------------------|---------|---------|
| <i>Right temporal lobe cortical thickness (mm)</i> | | | | |
| Temporal pole | 3.1667 ± 0.398 | 3.5167 ± 0.4 | -0.87 | 0.38 |
| Superior temporal | 2.5443 ± 0.143 | 2.7943 ± 0.157 | -1.59 | 0.11 |
| Middle temporal | 2.5725 ± 0.139 | 2.8029 ± 0.165 | -1.39 | 0.16 |
| Inferior temporal | 2.5174 ± 0.146 | 2.7478 ± 0.134 | -1.72 | 0.08 |
| Transverse temporal | 2.1749 ± 0.193 | 2.4249 ± 0.237 | -1.05 | 0.29 |
| Entorhinal cortex | 3.0864 ± 0.447 | 3.3168 ± 0.391 | -0.58 | 0.55 |
| Para-hippocampal | 2.4343 ± 0.256 | 2.6647 ± 0.204 | -1.12 | 0.25 |
| Fusiform | 2.4526 ± 0.162 | 2.683 ± 0.167 | -1.38 | 0.16 |
| Insula | 2.7825 ± 0.149 | 3.0325 ± 0.163 | -1.53 | 0.12 |
| <i>Right occipital lobe cortical thickness (mm)</i> | | | | |
| Lateral occipital | 1.9826 ± 0.115 | 2.213 ± 0.146 | -1.58 | 0.11 |
| Cuneus | 1.7185 ± 0.111 | 1.9489 ± 0.162 | -1.42 | 0.15 |
| Lingual cortex | 1.8828 ± 0.110 | 2.1132 ± 0.150 | -1.53 | 0.12 |
| Peri-calcarine cortex | 1.5034 ± 0.091 | 1.7338 ± 0.176 | -1.3 | 0.19 |

There was no significant difference in the cortical thickness of the left temporal lobe between the RRMS and control groups (Table 6).

XXIV. Cortical thickness results of the right occipital lobe

There was no significant difference in the cortical thickness of the left occipital lobe between the RRMS and control groups (Table 6).

XI. Areas of significant difference in cortical thickness in both hemispheres

There was significant decrease in the cortical thickness in the RRMS group compared to the control group in the precentral, paracentral, postcentral and posterior cingulate cortices in both hemispheres with Z-scores < -2 and P values < 0.05 .

XII. Whole brain vertex-based (GLM) analysis

After doing the whole brain point-by-point vertex group comparison of thickness across the cortical surface without any prior hypothesis, we found significant reduction of the cortical thickness in the precentral, postcentral, paracentral and posterior cingulate in both hemispheres (Fig. 1).

XII. Correlation between cortical thickness and EDSS scores

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

- The first subgroup had 7 patients representing 23.3% of the studied subjects with EDSS scores ranging from 1 to 2.5. This group had a significant but mild decreased thickness of the precentral, paracentral, postcentral and posterior cingulate cortices (PCC) in both hemispheres (Fig. 2).
- The second subgroup had 16 patients representing 53.3% of the studied subjects with EDSS scores ranging from 3 to 4.5. This group had a significant decreased thickness of the precentral, paracentral, postcentral, posterior cingulate cortices in both hemispheres and mean cortical thickness of both hemispheres (Fig. 3).
- The third subgroup had 7 patients representing 23.3% of the studied subjects with EDSS scores ranging from 5 to 6.5. This group had the most significant and most reduction of thickness of the precentral, paracentral, postcentral, posterior cingulate cortices in both hemispheres and mean cortical thickness of both hemispheres with atrophy patterns starting to affect other areas of the cortex as visual cortex and superior frontal cortex (Fig. 4).

According to this distribution and after calculating the correlation coefficients of the cortical thickness of brain areas and the mean cortical thickness of both hemispheres with the EDSS scores, we found that the mean cortical thickness of both hemispheres, precentral, paracentral, postcentral and posterior cingulate cortices in both hemispheres were negatively correlated with the EDSS scores with correlation coefficients ranging from -0.9878 to -0.7977 (Table 7, Figs. 5, 6).

Discussion

Multiple sclerosis is a chronic inflammatory demyelinating disease of the central nervous system [18]. Relapsing-remitting MS is the most common disease subtype and consists of relapses separated by periods of remission of variable length. After these alternating episodes of neurological disability and recovery, around 70% of the patients develop a secondary-progressive disease course which is characterized by progressive neurological decline [13].

In spite of the belief that MS is primarily a white matter disease, as early as 1962 pathologic studies had reported focal areas of cortical demyelination in MS patients and even reported cortical demyelinating lesions up to 26% of the total number of cerebral plaques [19].

Despite initial focus on white matter demyelination, there has been increasing focus on the gray matter pathology occurring in MS. This shift in focus was encouraged by new histochemical techniques which markedly increased the visibility of cortical lesions *ex vivo* [20].

New neuroimaging techniques like Double inversion recovery (DIR) improve the performance of FLAIR and T2 imaging; although DIR shows more sensitivity than FLAIR and T2 imaging, it still misses most of cortical lesions [21].

Measurement of cortical gray matter thickness has several advantages over detection of cortical lesions. Gray matter lesions are difficult to visualize even with advanced sequences, and there is significant variation between readers. Cortical Gray matter thickness measurements, on the other hand, are more sensitive and reliable with reproducible results among research institutions [22].

Different methods of cortical thickness measurements are now available, manual and automated methods, usually manual segmentation is limited to a certain area of the cortex rather than the fully automated methods which can do whole cortical segmentation. Different techniques are now used in the automated method as surface or voxel based or both [23].

Automated surface-based measures of cortical thickness have become the dominant standard in the brain imaging community [24].

FreeSurfer is an open-source software package developed by Harvard University that measures the thickness of the cortex in different brain regions using surface-based analysis techniques [25]. FreeSurfer's distance measure is to take the closest vertex on the opposite surface, then find that vertex' closest point, and average the two distances. Then, it uses Surface-based alignment, a tool to improved alignment of cortical thickness maps to increase the accuracy of localizing cortical thickness measures across subjects [13].

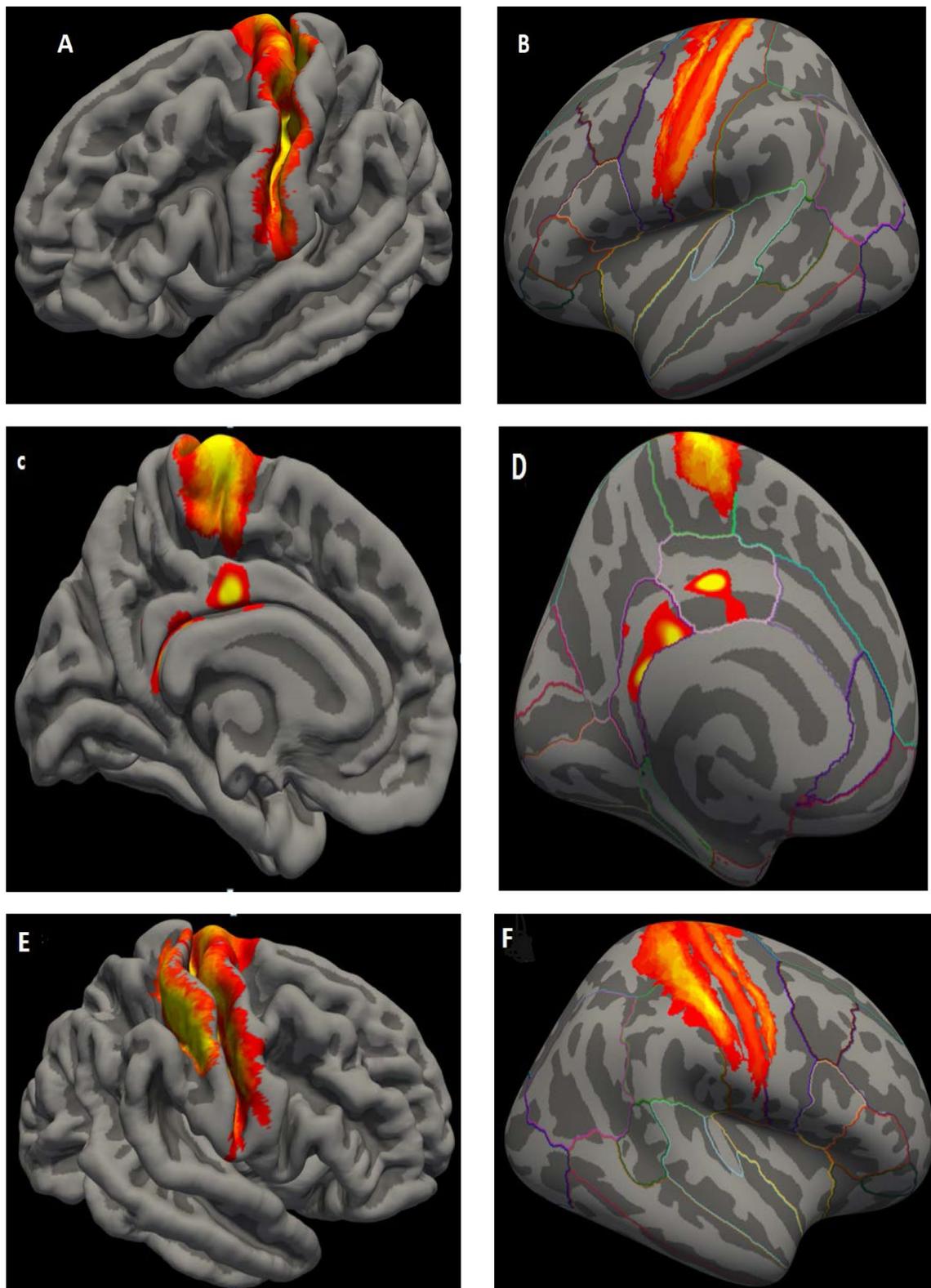


Fig. 1 Whole brain vertex-based (GLM) analysis showing the significant group differences of cortical thickness, displayed on **A** Lateral view of the left hemisphere surface template, **B** inflated view. The highlighted areas are precentral and postcentral cortex. **C** Medial view of the left hemisphere surface template, **D** inflated view. The highlighted areas are paracentral lobule and posterior cingulate cortex. **E** Lateral view of the right hemisphere surface template, **F** inflated view. The highlighted areas are precentral and postcentral cortex. **G** Medial view of the right hemisphere surface template, **H** inflated view. The highlighted areas are paracentral lobule and posterior cingulate cortex. Significance was set to a P value of < 0.05

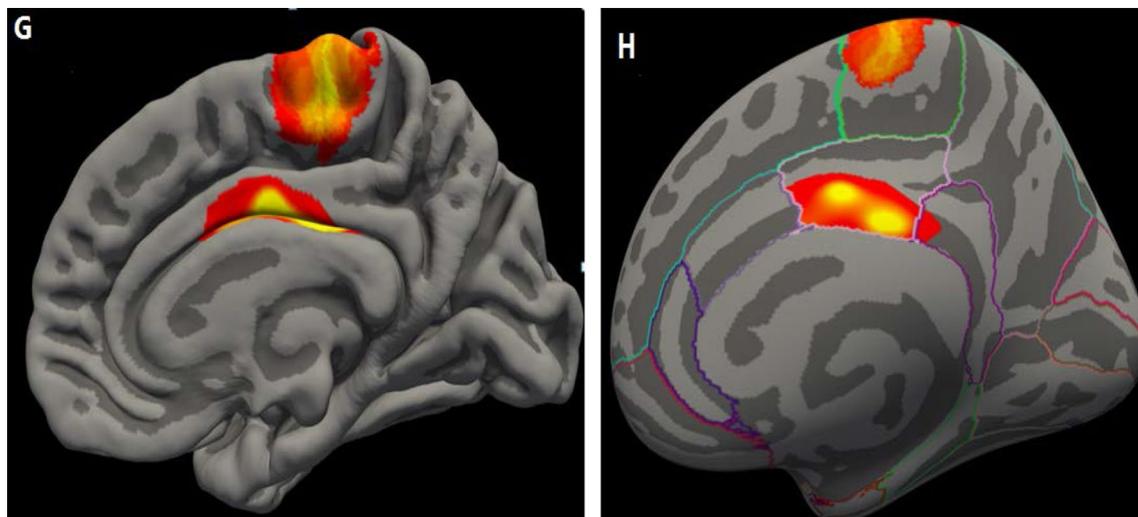


Fig. 1 continued

The general linear model (GLM) is the optimal statistical model used in morphometric brain studies. It has been used successfully in the analysis of the structures of the brain as it is flexible to analyze both continuous and categorical variables [26, 27].

Our study included 30 patients diagnosed with RRMS: 22 females and 8 males with ages ranging from 20 to 35 years and a mean age 27.54 years, and 30 control individuals with a mean age 26.42 years.

The studied patients group had variable degrees of clinical disability 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 patient in this study undertook a high-resolution thin cut 3D T1W SPGR sequence. Then, cortical thickness was measured using FreeSurfer software package. Next, we did whole brain vertex-based analysis is a point-by-point group comparison of thickness across the cortical surface, without any prior hypothesis, starting with the average images of each group.

After cortical thickness measurement, we found that there is a significant decrease in the cortical thickness in the RRMS group compared to the control group in the mean cortical thickness of the left and right hemispheres, and found focal thickness reduction in precentral, paracentral, postcentral and posterior cingulate cortices in both hemispheres.

We subdivided our studied group of patients into three subgroups based on their EDSS scores; the first subgroup represented 23.3% of the total patient's group, they had EDSS scores ranging from 1 to 2.5 and they showed significant but mild decreased thickness of the precentral, paracentral, postcentral and posterior cingulate cortices

in both hemispheres. The second subgroup represented 53.3% of the total patient's group, they had EDSS scores ranging from 3 to 4.5 and showed significant decreased thickness of the precentral, paracentral, postcentral, posterior cingulate cortices in both hemispheres and mean cortical thickness of both hemispheres. The third subgroup represented 23.3% of the total patient's group, they had EDSS scores ranging from 5 to 6.5 and showed the most significant and most reduction of thickness of the precentral, paracentral, postcentral, posterior cingulate cortices in both hemispheres and mean cortical thickness of both hemispheres with atrophy patterns starting to affect other areas of the cortex as visual cortex and superior frontal cortex.

Based on the results of these subdivisions and calculating the correlation coefficients, we found that the mean cortical thickness of both hemispheres, precentral, paracentral, postcentral, and posterior cingulate cortices in both hemispheres were negatively correlated with the EDSS scores with correlation coefficients ranging from -0.9878 to -0.7977 . These findings indicate that physical dysfunction, as measured by higher EDSS scores, was predicted by atrophy of the bilateral sensorimotor cortex, PCC, and global cortical thickness reduction.

The reduction of the mean cortical thickness observed in our study is a key finding in understanding the disease burden and pathology, as it shows that cortical gray matter is affected in MS. Studies used 7 T scanners reported that there is a huge disease burden in the cortical gray matter of MS patients. The possibility to detect this pathology in 1.5 T scanners is very crucial in the clinical setting as it is the most available scanners in the clinical arena [28].

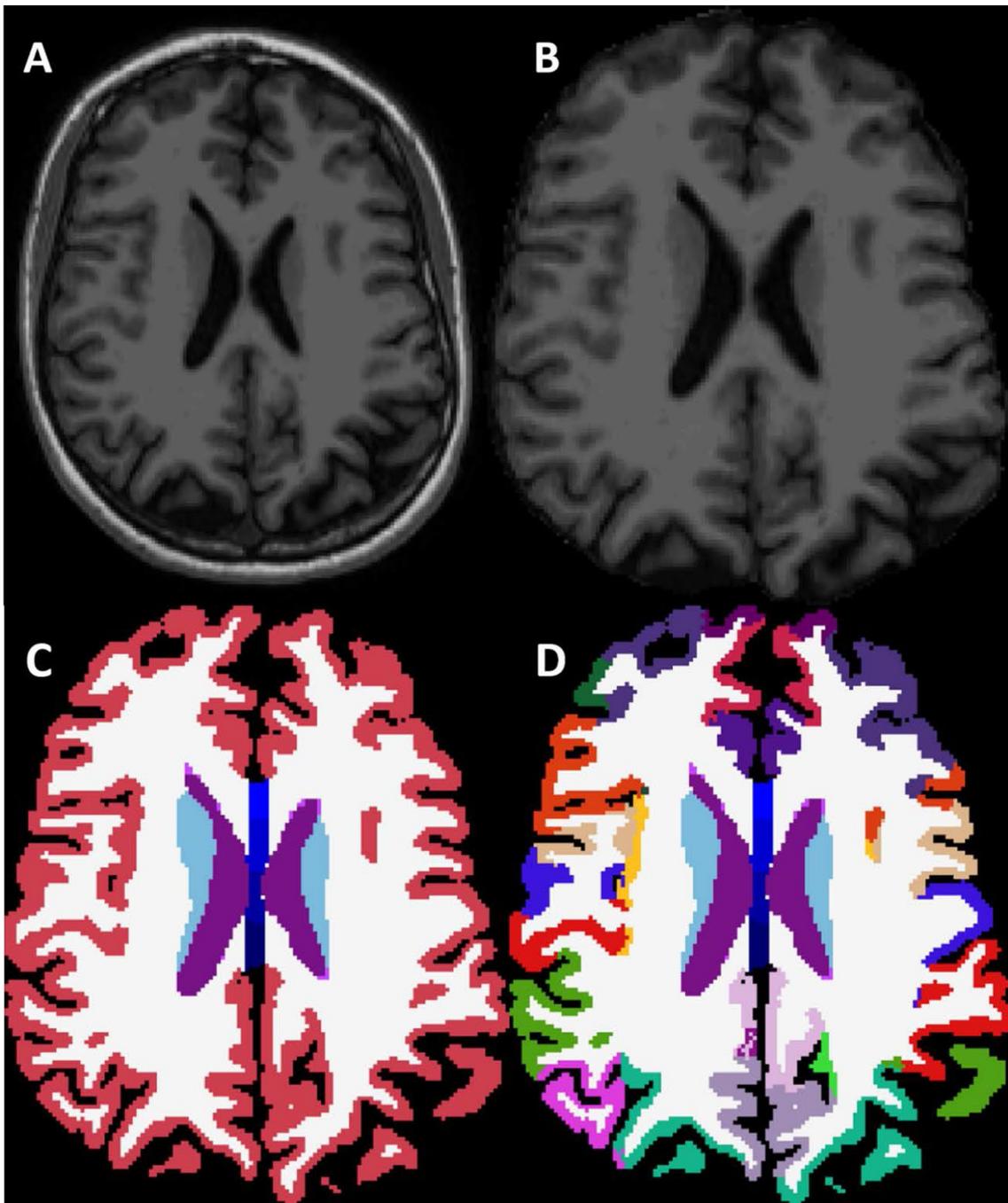


Fig. 2 A female patient aged 29 years old, known to have RRMS with EDSS score of 2.5. I. Cortex segmentation: raw T1WI axial plane (A), T1W image after brain extraction (B), gray and white matter segmentation (C) and cortex segmentation (D). II. Surface reconstruction: T1W image with pial surface (red line) and white matter surface (yellow line) (E) and surface reconstruction (F). III. Cortical thickness results in mm: The patient had significant decrease in cortical thickness of the precentral (1.9475 mm, 1.9151 mm), postcentral (1.5531 mm, 1.4447 mm), paracentral (1.8846 mm, 1.9118 mm) and posterior cingulate cortices (1.8251 mm, 2.1117 mm) in left and right side, respectively

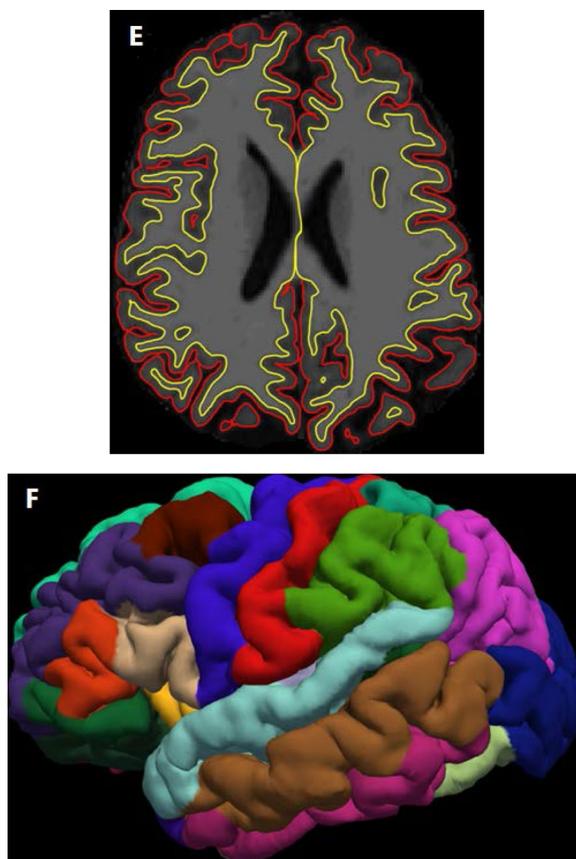


Fig. 2 continued

It is worth mentioning that we found that there was affection of other cortical areas in the patients who had EDSS scores of 5 or more. This shows that cortical gray matter affection is increased with disability progression.

Lots of studies used cortical thickness measurements to investigate cortical affection in MS. Steenwijk et al. [29] studied cortical atrophy patterns in multiple sclerosis. They investigated whether gray matter atrophy in multiple sclerosis is a more diffuse 'global' process or develops, instead, according to clearly distinct anatomical patterns.

They found that several cortical thickness patterns were differently loaded in patients with multiple sclerosis compared with healthy controls. The patterns relevant for multiple sclerosis were largely symmetric and the degree to which they occurred in patients correlated with clinical dysfunction [29].

Our study is consistent with their findings as they found that higher EDSS scores, was predicted by atrophy of the bilateral sensorimotor cortex and global atrophy despite the absence of an absolute difference in white matter lesion load between patients with multiple sclerosis and controls.

These findings were in confirmation with Narayana et al. [30], who found that there is a strong association between physical dysfunction and atrophy in the sensorimotor cortex.

Schoonheim et al. [31] found that posterior cingulate cortex and bilateral temporal pole atrophy predicted Cognitive dysfunction and information processing speed.

In multiple sclerosis, these areas are known for their significant role in cognitive dysfunction, while in our work we did not find significant affection of the temporal poles.

Furthermore, a study by Louapre et al. [32] revealed that the interruption in the default mode network was strongly predicted by the posterior cingulate cortex atrophy in MS patients with cognitive impaired. Based on this, the authors even proposed that default mode network disconnection may remove the compensatory mechanism that MS patients use to adjust the widespread damage in the brain.

Van den Heuvel et al. [33] tried to explain why non-random cortical atrophy patterns were observed in multiple sclerosis. They hypothesize that, after local gray

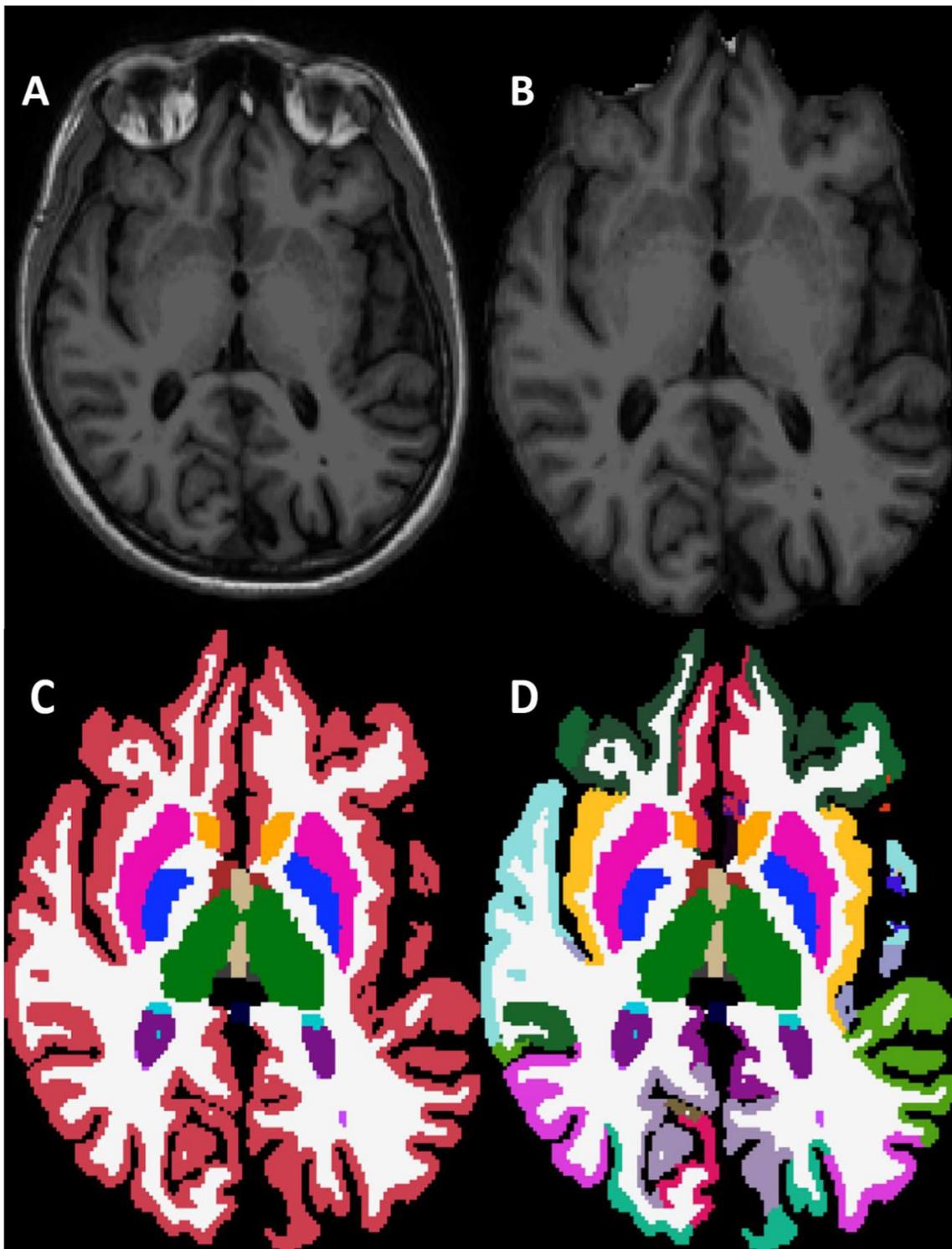


Fig. 3 A female patient aged 24 years old, known to have RRMS with EDSS score of 3. I. Cortex segmentation: raw T1WI axial plane (A), T1W image after brain extraction (B), gray and white matter segmentation (C) and cortex segmentation (D). II. Surface reconstruction: T1W image with pial surface (red line) and white matter surface (yellow line) (E) and surface reconstruction (F). III. Cortical thickness results in mm: The patient had significant decrease in the mean cortical thickness (1.848 mm, 1.944 mm), and the precentral (1.7775 mm, 1.8151 mm), postcentral (1.3831 mm, 1.4447 mm), paracentral (1.7146 mm, 1.8118 mm) and posterior cingulate cortices (1.7551 mm, 1.7117 mm) in left and right side, respectively

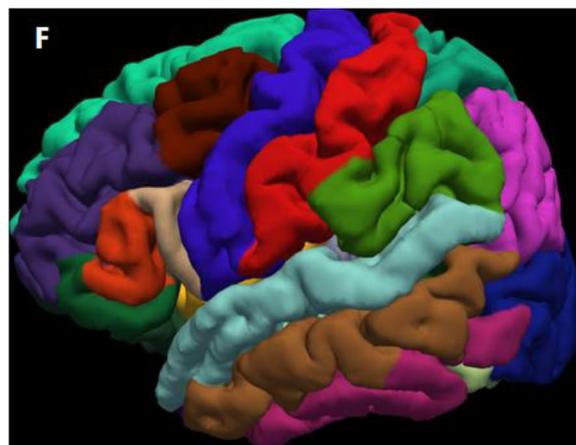
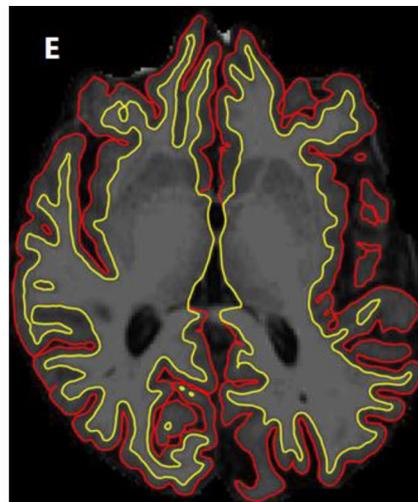


Fig. 3 continued

matter pathology starts, a second-order effect follows that causes atrophy in other anatomically connected gray matter areas. This would explain why the cortical atrophy patterns were mostly located in cortical regions known as ‘network hubs’ in the brain (e.g., posterior cingulate) due to their central position in the structural network these regions are particularly sensitive to atrophy and pathology elsewhere in the brain [34].

This theory is promising as it can explain also the weaker relationship between gray matter atrophy and white matter pathology that was previously observed in the patients with progressive multiple sclerosis [34].

Our study agrees with this theory by observing the decreased thickness of the posterior cingulate cortex, a known central hub in the default mode network.

In addition to cortical thickness measurement studies, it is interesting to find that functional MRI studies found that there was reduction of activity and functional connectivity of the default mode network. A finding that

matches our work as we found reduction of the cortical thickness of the posterior cingulate cortex that is a dominant part of that functional network [35, 36].

There are other different methods of MRI brain segmentation applied in MS patients as whole gray and white matter segmentation, white matter lesion volume, cerebellum and brain stem volume and subcortical gray matter segmentation [37, 38].

The uniqueness of the current study is investigating cortical thickness changes in different brain areas rather than whole gray matter measurement enabling us to see if there is focal rather than generalized cortical affection.

In our study, we implemented a widely used fully automated segmentation software, limiting the human (operator) interaction and bias in imaging segmentation, make it possible to replicate the finding and compare our results relative to other studies using the same technique.

Unsupervised fully automated segmentation is not without side effects as there may be segmentation errors

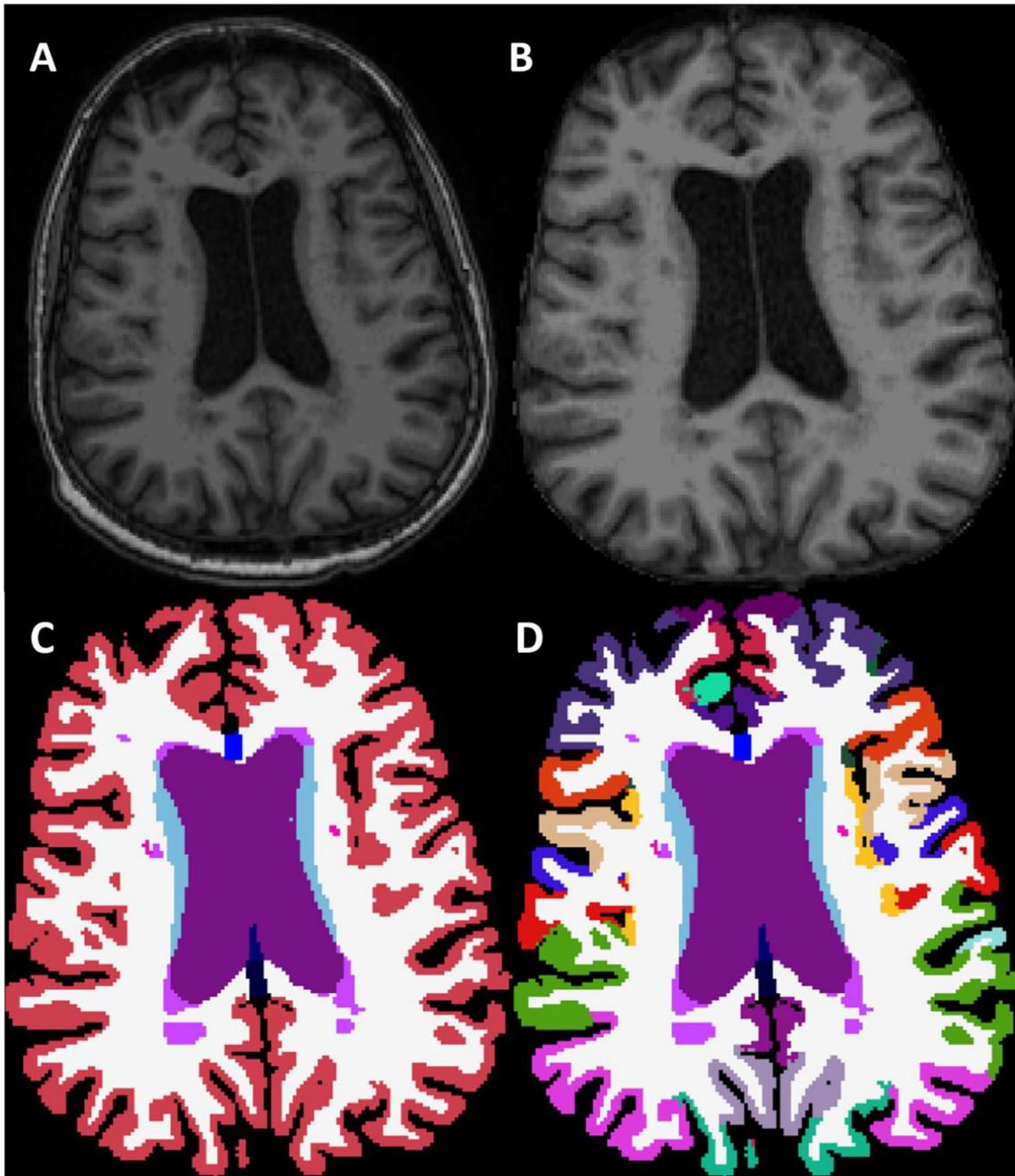


Fig. 4 A female patient aged 27 years old, known to have RRMS with EDSS score of 6. I. Cortex segmentation: raw T1WI axial plane (A), T1W image after brain extraction (B), gray and white matter segmentation (C) and cortex segmentation (D). II. Surface reconstruction: T1W image with pial surface (red line) and white matter surface (yellow line) (E) and surface reconstruction (F). III. Cortical thickness results in mm: The patient had significant decrease in the mean cortical thickness (1.848 mm, 1.984 mm), and the precentral (1.4775 mm, 1.4551 mm), postcentral (1.2831 mm, 1.3847 mm), paracental (1.5146 mm, 1.6518 mm) and posterior cingulate cortices (1.7551 mm, 1.8517 mm) in left and right side, respectively, and left Inferior Temporal (1.7343 mm) and left Lateral Occipital (1.6943 mm) cortices

[39]; but in our study, we checked the segmentation available in the Freesurfer software package to check, in every patient; if errors were detected, we used a tool

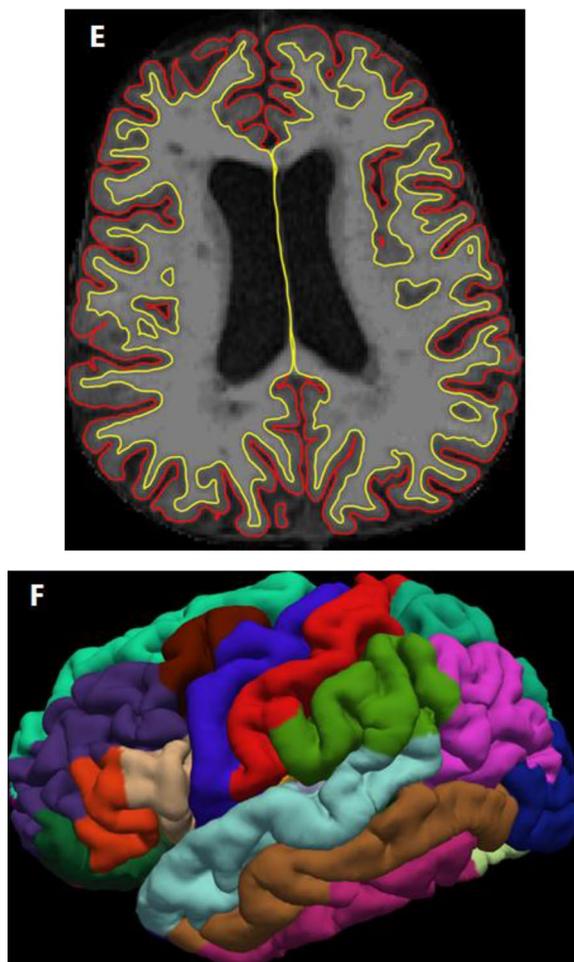


Fig. 4 continued

edit and correct these errors and reevaluate the thickness measurement.

Table 7 The correlation coefficient values demonstrating the correlation between cortical thickness and EDSS scores

| Structure | Pearson correlation coefficient |
|---|---------------------------------|
| Mean cortical thickness of the left hemisphere | -0.9833 |
| Left precentral | -0.9708 |
| Left postcentral | -0.8433 |
| Left paracentral | -0.9878 |
| Left posterior cingulate | -0.987 |
| Mean cortical thickness of the right hemisphere | -0.914 |
| Right precentral | -0.9231 |
| Right postcentral | -0.7977 |
| Right paracentral | -0.9187 |
| Right posterior cingulate | -0.9651 |

Limitation of the study

Firstly, the relatively small sample size can produce type I error and can miss subtle differences between the patients and controls. A second limitation is the exclusion of subcortical and cerebellar gray matter from the current work. Lack of longitudinal study is also a major limitation as it will show us the dynamic correlation between disease progression, disability and brain atrophy which can be diffuse or local process; however, this could not be done in the current study.

Another limit of our study lies in the heterogeneity of the patient group in terms of clinical variables, which facilitated the detection of potential correlates of EDSS and cortical thickness, but in turn limited the current approach to the study of the common patterns of brain tissue involvement across a heterogeneous population,

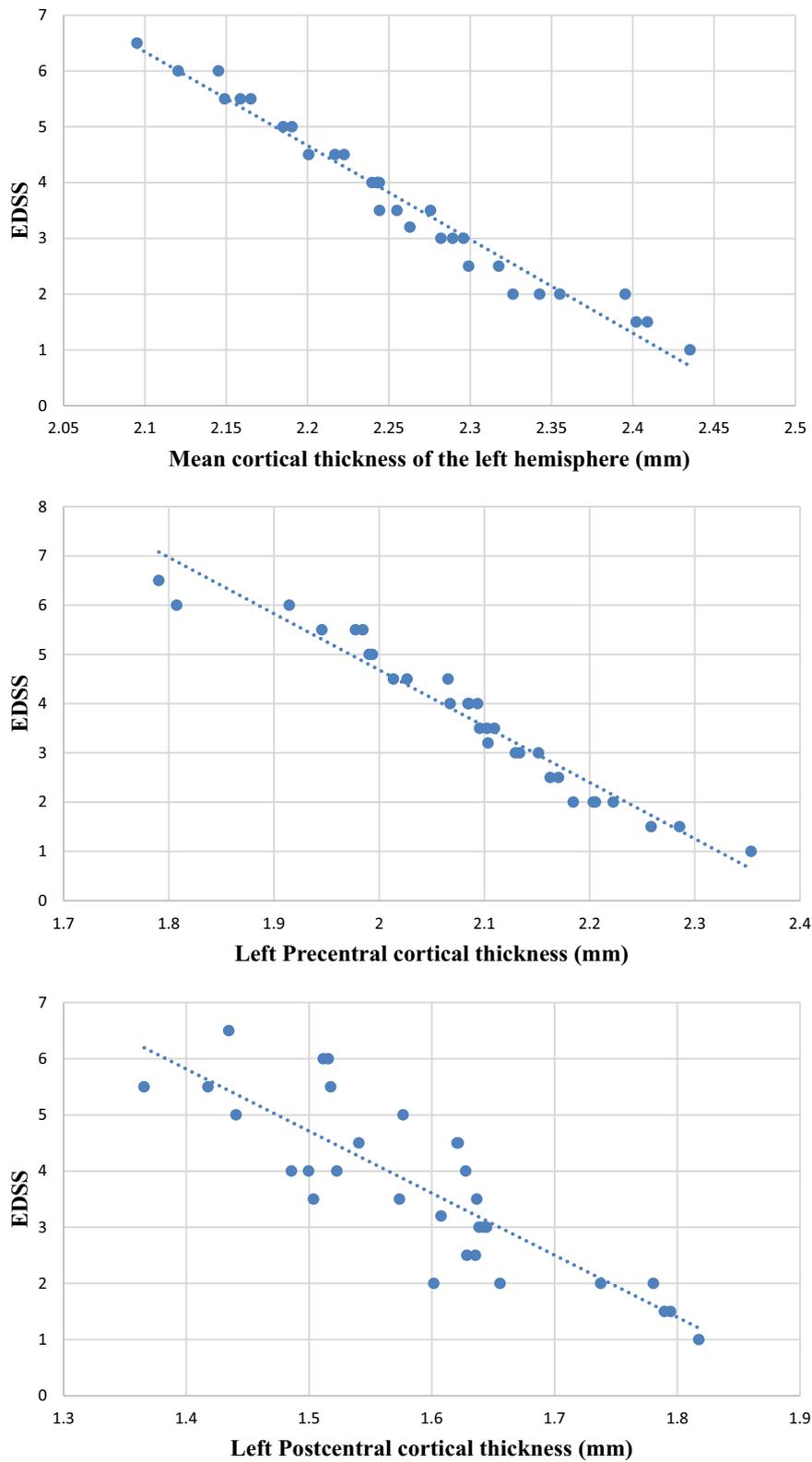


Fig. 5 Correlation between the mean cortical thickness of the left hemisphere, the left precentral, postcentral, paracentral, posterior cingulate cortical thickness and EDSS scores

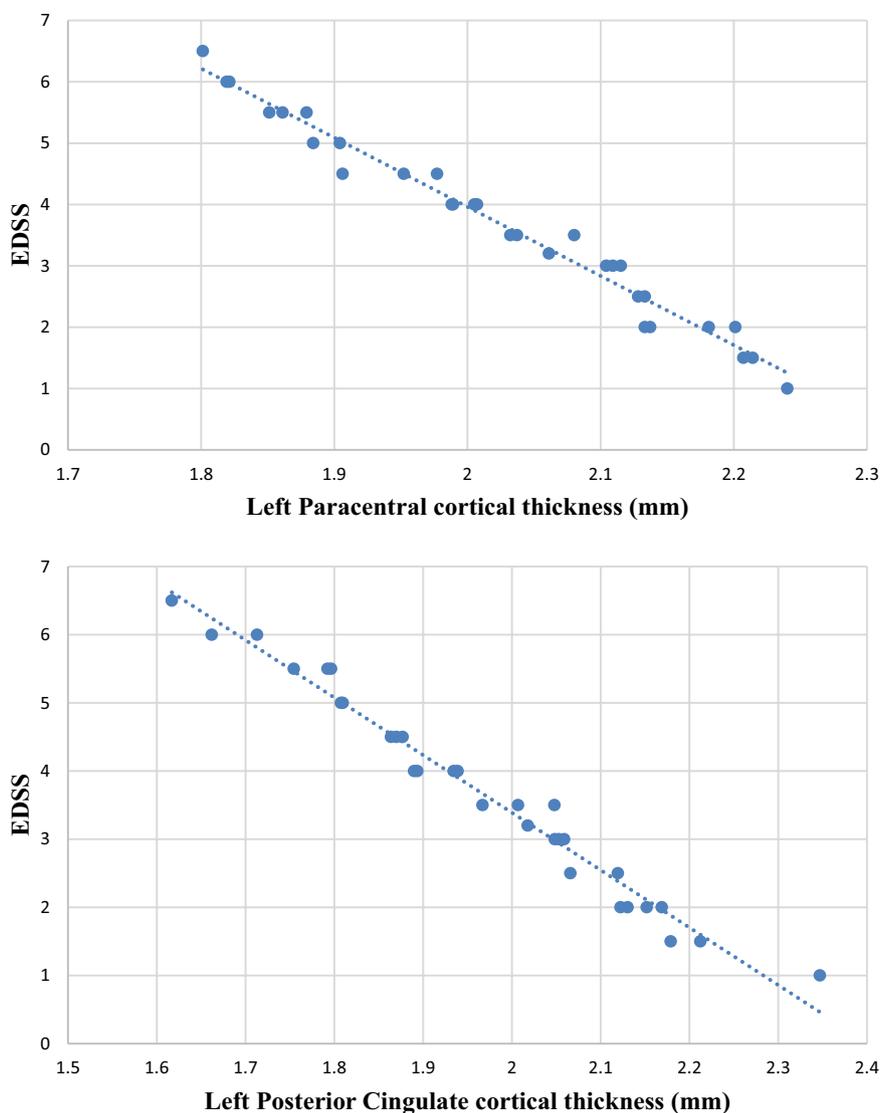


Fig. 5 continued

while correlations that may be present only in MS subgroups (e.g., early MS, benign MS) may have remained undetected.

Recommendation

Future studies on this subject can benefit from including other subtypes of MS, as PPMS and SPMS, which can aid specific patterns of the cortical gray matter affection related to each subtype, another recommendation is to use higher magnet scanners as 3 T or 7 T to investigate if there any correlation between the site of cortical lesions and the areas of cortical thickness reduction.

It is also important to use other advanced imaging techniques such as Diffusion tensor imaging (DTI), and

functional magnetic resonance imaging (fMRI), either resting-state or task-based, to have another perspective in the pathology and brain affection detected by MRI.

Conclusions

MRI and post-processing segmentation analysis are non-invasive imaging techniques that proved to be useful in evaluation of cortical gray matter. It can capture ongoing hidden pathological activity in the clinical practice. The cortical thickness affection is correlated with the level of clinical disability measured by EDSS score. Additional longitudinal studies are needed to follow the cortical gray matter changes over time.

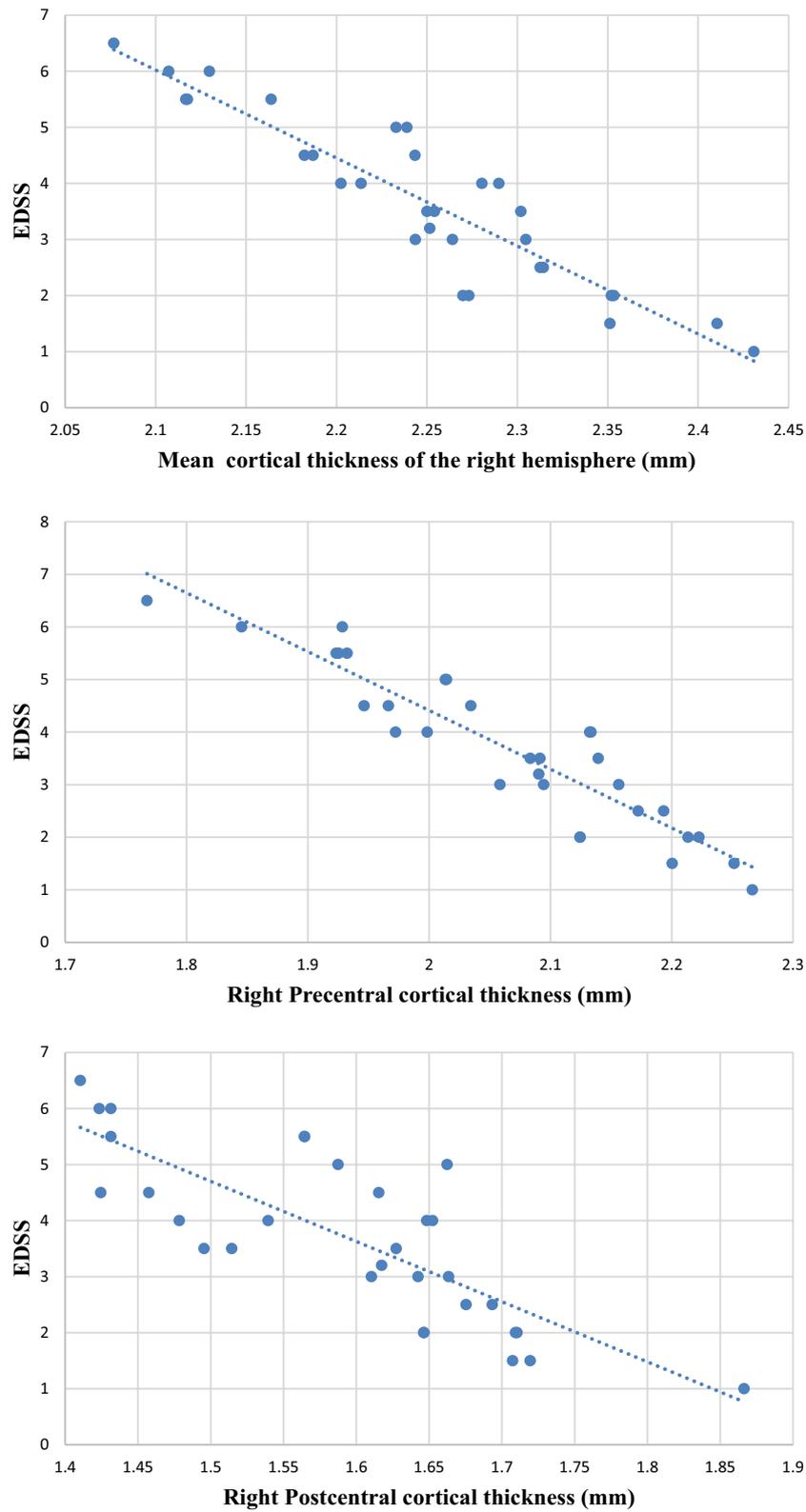


Fig. 6 Correlation between the mean cortical thickness of the right hemisphere, the right precentral, postcentral, paracentral, posterior cingulate cortical thickness and EDSS scores

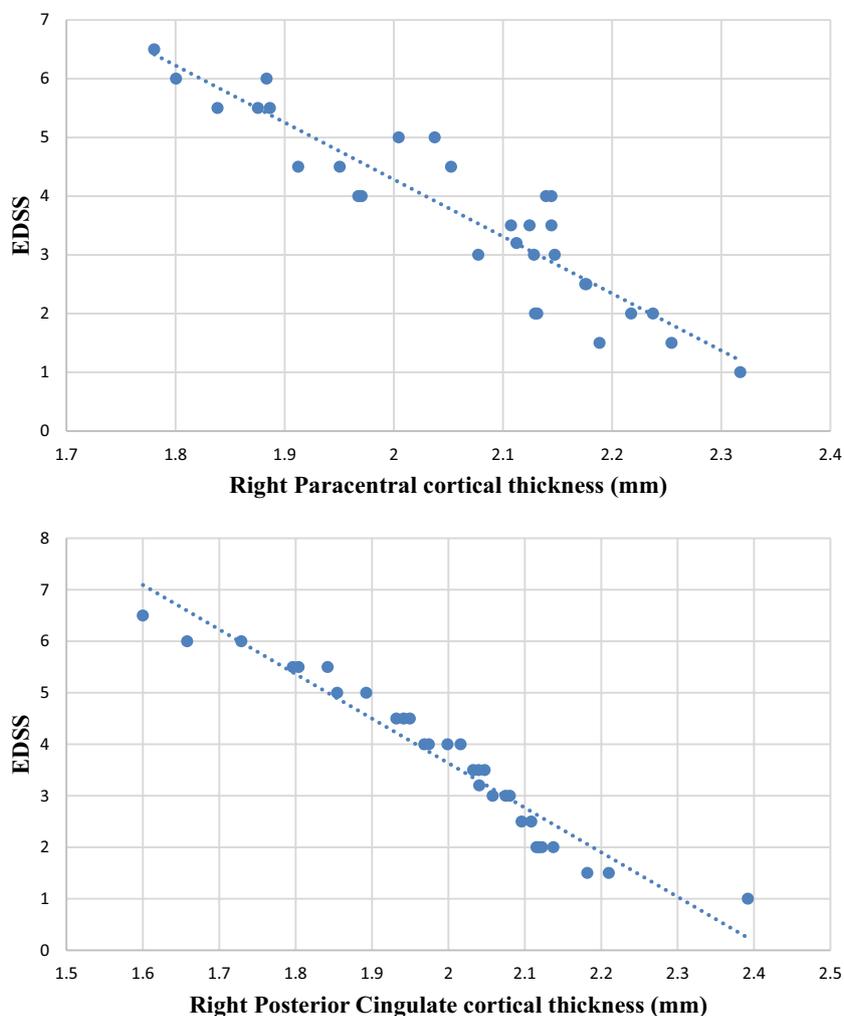


Fig. 6 continued

Abbreviations

EDSS: Expanded disability status scale; MS: Multiple sclerosis; RRMS: Relapsing remission relapse; SPGR: Sagittal 3D T1-weighted spoiled gradient; GM: Gray matter; FLAIR: Fluid attenuation inversion recovery; DIR: Double Inversion Recovery; GLM: Vertex-based General Linear Model.

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Authors' contributions

MB 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, MB supervised the study with significant contribution to design the methodology, manuscript revision and preparation. MK correlated the clinical data of patient, matched it with the findings, and 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 ad 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 (31543/05/17).

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 of interest

The authors declare that they have no competing of interests.

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