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Research Paper

Cortical thickness and surface area relate to specific symptoms in early relapsing–remitting multiple sclerosis

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Abstract

Background: Cortical atrophy is common in early relapsing–remitting multiple sclerosis (RRMS). Whether this atrophy is caused by changes in cortical thickness or cortical surface area is not known, nor is their separate contributions to clinical symptoms.

Objectives: To investigate the difference in cortical surface area, thickness and volume between early RRMS patients and healthy controls; and the relationship between these measures and neurological disability, cognitive decline, fatigue and depression.

Methods: RRMS patients ($n = 61$) underwent magnetic resonance imaging (MRI), neurological and neuropsychological examinations. We estimated cortical surface area, thickness and volume and compared them with matched healthy controls ($n = 61$). We estimated the correlations between clinical symptoms and cortical measures within the patient group.

Results: We found no differences in cortical surface area, but widespread differences in cortical thickness and volume between the groups. Neurological disability was related to regionally smaller cortical thickness and volume. Better verbal memory was related to regionally larger surface area; and better visuo-spatial memory, to regionally larger cortical volume. Higher depression scores and fatigue were associated with regionally smaller cortical surface area and volume.

Conclusions: We found that cortical thickness, but not cortical surface area, is affected in early RRMS. We identified specific structural correlates to the main clinical symptoms in early RRMS.

Keywords: Brain function, cerebral cortex, cortical surface area, cortical thickness, depression, fatigue, magnetic resonance imaging, multiple sclerosis, neurological disability, relapsing–remitting multiple sclerosis, symptoms

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Introduction

Cortical grey matter (GM) atrophy is a well-documented feature of multiple sclerosis (MS), usually measured as reductions in either cortical thickness or cortical volume.[1–5] Cortical volume reductions may be caused either by a reduction in cortical surface area, a reduction in the cortical thickness, or both.

Cortical thickness and surface area are affected differently across the normal life span.[6] Twin studies reveal that cortical thickness and cortical surface area are both highly heritable, but that they are inherited by a different set of genes.[7] We hypothesized that the main difference in cortical structure between early relapsing–remitting MS (RRMS) patients and healthy controls would be similar to that seen in neurodegenerative diseases,[8,9] i.e. with cortical thickness differences, but not affecting cortical surface area. Furthermore, we aimed to examine whether neurological disability, cognition, fatigue and depression scores in our patient group correlated with cortical surface area, cortical thickness or cortical volume.

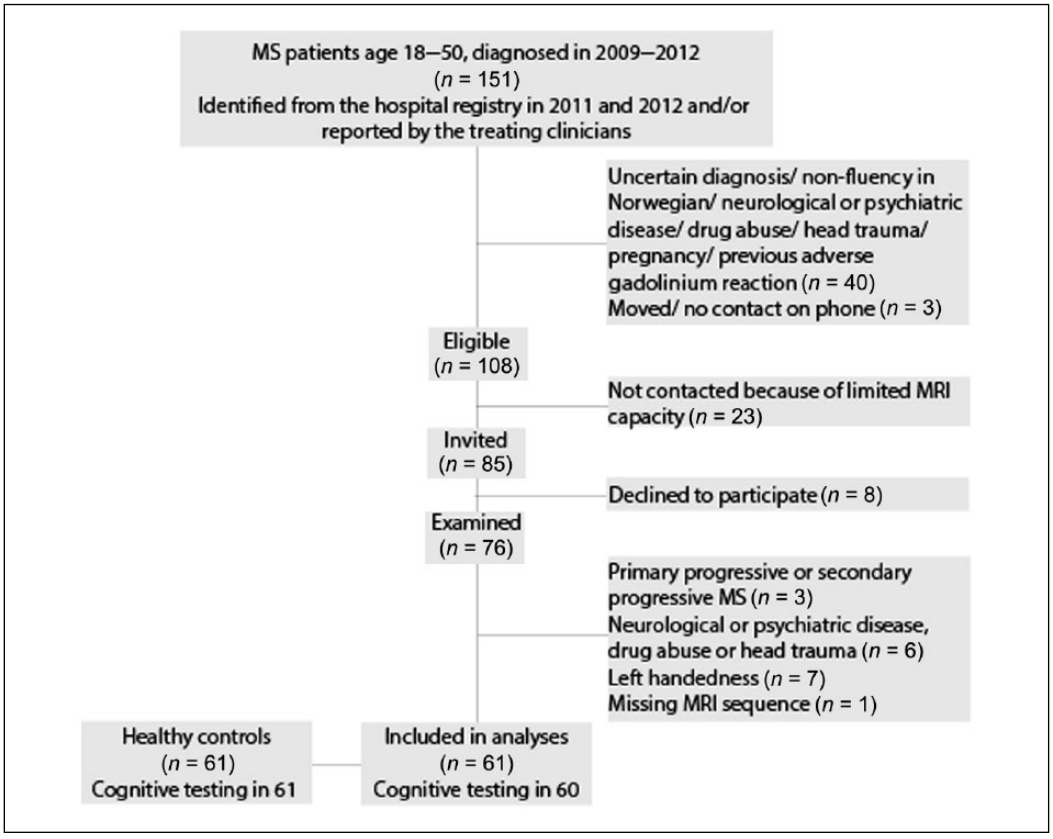


Figure 1. Flow chart of patient selection.
Inclusion criteria for the patients were: age 18–50, no more than 3 years since diagnosis of RRMS, at least 6 weeks since the last relapse or corticoid treatment, fluency in the Norwegian language, right handedness, no prior neurological or psychiatric disease, no head injury and no substance abuse. We also excluded pregnant or breastfeeding patients, and a patient with a previous adverse reaction to gadolinium injection. One of the authors, blinded to the test results, was in charge of selecting the controls. Like the patients, the controls were fluent in the Norwegian language, right handed, and without a history of neurological or psychiatric disease, head injury or drug abuse.
MRI: Magnetic resonance imaging; MS: multiple sclerosis; RRMS: relapsing–remitting multiple sclerosis.

In Oslo, Norway, most neurological investigations and treatments are offered within the public health care system, and the patients are enrolled in patient registries. The present study was designed to take advantage of this unselected patient pool, to study detailed imaging characteristics of cortical structure in recently-diagnosed RRMS patients compared to matched healthy controls, and aimed to identify structural cortical differences in the early phase of MS and their relation to clinical symptoms.

Materials and methods

Patients and controls

Patients diagnosed with RRMS according to the revised McDonald Criteria[10] in the period from January 2009 to October 2012 at Oslo University Hospital, Ullevål, Norway, were considered for participation in the study. The project was approved by the local ethics committees, and the participants received oral and written information, and gave written informed consent. Figure 1 shows our flow chart for patient selection. The controls were matched by age and gender on a group level, selected from the ongoing project 'Cognition and plasticity through the lifespan' at the Institute of Psychology, University of Oslo. Details concerning the controls are described elsewhere.[11]

Neurological, neuropsychological and neuropsychiatric evaluation

The patients underwent a full neurological examination by the same trained physician, within the same week as their magnetic resonance imaging (MRI) examination. Both patients and controls underwent testing of general abilities with the

vocabulary and matrix reasoning subsets of the Wechsler Abbreviated Scale of Intelligence.[12] We included neuropsychological assessment with the written version of the Symbol Digit Modalities Test[13] for *processing speed*, the sum score of the first five trials of the California Verbal Learning Test 2[14] for *verbal memory* and the sum score of the first three trials of the Brief Visuospatial Memory Test Revised,[15] for *visuospatial memory*. We applied the raw scores of the tests in the analyses.

Fatigue symptoms in the RRMS group were measured with the self-reporting Fatigue Severity Scale (FSS), constructed for monitoring fatigue in chronic neurological diseases.[16] Depressive symptoms were measured with the self-reporting questionnaire, Beck Depression Inventory 2 (BDI),[17] which is a general depression scale validated for patients with MS. We excluded controls whom scored > 16 on the BDI.

Image acquisition

Our patients and controls underwent MRI examinations using the same 1.5 T Siemens Avanto scanner (Siemens Medical Solutions) with a 12-channel head coil. We scanned the controls between June 2007 and December 2008, and the patients between January 2012 and January 2013. The Magnetization Prepared Rapid Gradient Echo (MP-RAGE) sequences were kept identical between the scanning periods. We used 3-dimensional T1-weighted MP-RAGE sequences for surface-based and volumetric analyses, and combined the MP-RAGE and the Fluid-Attenuated Inversion Recovery (FLAIR) sequence to estimate the white matter (WM) lesion load. Details concerning the sequences are provided online. Please see Appendix (supplementary data).

Image analyses

We calculated WM lesion load using Cascade,[18] an automatic algorithm developed at Karolinska Institute in Stockholm, Sweden (http://ki.se/en/nvs/cascade). We used two MRI sequences (MP-RAGE and FLAIR) as input for the image analyses. Please see Appendix (supplementary data, online).

We used the FreeSurfer version 5.1 (http://surfer.nmr.mgh.harvard.edu) for quantification of cortical GM characteristics. Detailed descriptions of the methods are given elsewhere,[6,19–21] and online (see Appendix, supplementary data).

Statistical analysis

We used PASW Statistics version 20.0 (SPSS, Chicago, IL) for statistical analyses. We analyzed the differences between patients and controls using independent samples *T*-tests. One-sample *T*-tests were used to test the neuropsychological test results of the patients against the normal material supplied in the respective test manuals (ref 13–15). We used Pearson's correlation analyses to test the null hypothesis that there were no associations between global cortical structure and demographic, clinical or MRI parameters.

For the surface-based analyses, we fitted a general linear model at each vertex, using cortical surface area, thickness and volume as dependent variables. The differences between patients and controls were investigated, using gender and age as covariates. The results were tested against an empirical null distribution of maximum cluster size across 10,000 iterations, using Z Monte Carlo simulations synthesized with a cluster-forming threshold of $p < 0.05$ (2-sided), yielding clusters corrected for multiple comparisons across the surface.

Corresponding analyses were done for the associations between the clinical manifestations and brain structure within the patient sample: We now applied the general linear model to investigate the effects of clinical variables, using gender, age and disease duration as covariates. Neurological disability, processing speed, verbal and visuospatial memory, fatigue and depression scores were independent variables included in separate analyses.

Results

Demographics, clinical and neuropsychological evaluation

The demographic characteristics of the 61 patients and 61 controls that we included in this study are summarized in Table 1(a).

The patients and controls had similar levels of general abilities (Table 2(a)), with a non-significant trend towards higher scores in the patient group, driven by higher vocabulary scores (data not shown). The patient group performed either 'as good as' or better than the norm on processing speed, verbal and visuospatial memory (Table 2(a)). The proportion of patients scoring below 1.5 standard deviations (SD) on the neuropsychological tests was within the range expected in a healthy sample. Only one person scored below 1.5 SD on two cognitive tests, and none scored below 1.5 SD on all three tests (data not shown). The

Table 1. Demographic and clinical characteristics of patients and controls.

Variable	Patients ($n = 61$)	Controls ($n = 61$)	Difference (95% CI)
(a) Demographic characteristics			
Gender (% female)	77	77	
Age, mean years (SD)	34.2 (7.1)	33.5 (8.4)	–2.06 – 3.52
Age, min-max	21–48	20–51	
Education			
Mean years (SD)	14.9 (2.2)	16.1 (2.5)	0.30–1.99
Min-max	9–21	9–23	
≥15 years education (%)	71	82	
(b) Clinical evaluation			
Neurological disability			
EDSS, mean (SD)	1.9 (0.7)		
Median	2		
Min-max	0–4		
Number of attacks, mean (SD)	1.8 (0.8)		
Median	2		
Min-max	1–5		
Disease-modulating treatment			
None (%)	21		
First line (%)	66		
Second line (%)	13		
Time since diagnosis			
Mean, months (SD)	14.4 (10.1)		
Min-max	1–34		
Disease duration			
Mean, months (SD)	26.0 (23.0)		
Min-max	3–128		
Working status (%)			
Unemployed	0		
Sick leave	7		
Student	16		
Part-time work	29		
Full-time work	43		
Maternity leave	5		

CI: 95% Confidence interval of the difference between the groups; EDSS: Expanded Disability Status Scale; first line disease modulatory treatment: Glatiramer acetate/interferons; min-max: minimum to maximum range; second line disease modulatory treatment: natalizumab/fingolimod.

patient group was therefore considered cognitively intact.

Global imaging parameters in patients and controls

The patients and controls had similar intracranial volumes and cerebral WM volumes. Total cortical surface area was similar between the groups; however, mean cortical thickness was 3.3% thinner and total cortical volume was 6.5% smaller in the patient group. The WM lesion load was calculated for the patients only: It revealed their WM lesion load was 5.75 mL (Table 2(b)). The total cortical surface area was not associated with age, but it was negatively related to gender (patients: $r = -0.58$; $p < 0.01$ and controls: $r = -0.38$; $p < 0.01$). Furthermore, in the patient group, the cortical surface area was negatively associated with their depression score ($r = -0.29$; $p = 0.03$) and intracranial volume ($r = 0.80$; $p < 0.01$), and

Table 2. Neuropsychological and global imaging characteristics of patients and controls.

Variable	Patients (n = 61)	Controls (n = 61)	Difference (95% CI)
(a) Neuropsychological evaluation[g]			
General ability level[a]			
Mean IQ (SD)	118.8 (11.6)	115.6 (8.9)	–0.56–6.89
Min-max	76–136	95–132	
Depression score[b,e]			
Mean BDI (SD)	8.4 (5.9)	3.9 (4.0)	2.61–6.31
Min-max	0–24	0–16	
% BDI >12[b]	27.1	6.9	
Fatigue score[b]			
Mean FSS (SD)	4.1 (1.7)	–	
Min-max	1–7	–	
% FSS > 4	49.2	–	
Processing speed[c]			
Mean z score (SD)	–0.21 (1.04)	–	–0.48–0.06
Min-max	–2.42–3.10	–	
Verbal memory[c]			
Mean T score (SD)	62.6 (12.6)	–	59.41–65.89
Min-max	32–83	–	
Visuospatial memory[c]			
Mean T score (SD)	53.9 (11.0)	–	51.02–56.68
Min-max	10–69	–	
(b) Global imaging parameters			
WM lesion volume[d]			
Mean mL (SD)	5.62 (3.49)	–	
Min-max	0.58–19.3	–	
Intracranial volume			
Mean mL (SD)	1569 (136)	1600 (124)	–78–15
Min-max	1303–1978	1403–1940	
Cerebral WM volume			
Mean mL (SD)	520 (52)	516 (56)	–15–23
Min-max	407–645	411–762	
Cortical surface area			
Mean cm^2	1706 (139)	1743 (131)	–85–12
Min-max	1458–2095	1543–2170	
Cortical thickness			
Mean mm (SD)	2.47 (0.098)	2.55 (0.098)	0.049–0.121
Min-max	2.20–2.68	2.31–2.81	
Cortical volume			
Mean mL (SD)	453.97 (36.26)	485.46 (34.29)	18.84–44.14
Min-max	378.71–551.55	409.64–553.29	

[a]60 patients/61 controls.
[b]59 patients/58 controls.
[c]60 patients.
[d]59 patients.
[e]Depression score equals sum of BDI, cut-off for proportion with depressive symptoms at BDI > 12.
[f]Fatigue equals mean of FSS, with cut-off for proportion with fatigue FSS > 4. Characteristics of the patients and controls were compared using independent samples *T*-test.
[g]For the neuropsychological evaluation, one sample continuous variables were compared with the norm, using one sample T-Test.
BDI: Beck Depression Inventory 2; FSS: Fatigue Severity Scale; IQ: intelligence quotient; mL: milliliter; WM: white matter.

Table 3. Correlations between whole brain imaging parameters and clinical and MRI parameters.

	Cortical surface area[a]	Cortical thickness	Cortical volume[a]	WM lesion volume[a]
	r, *p* (*n*)	r, *p* (*n*)	r, *p* (*n*)	r, *p* (*n*)
(a) Clinical evaluation				
Neurological disability[b]	–0.03, 0.82 (61)	–0.08, 0.54 (61)	–0.06, 0.66 (61)	**0.30, 0.02 (59)**
Attacks (*n*)	–0.15, 0.27 (61)	–0.15, 0.26 (61)	–0.23, 0.08 (61)	0.06, 0.67 (59)
Disease duration	0.10, 0.47 (61)	0.014, 0.92 (61)	0.06, 0.63 (61)	0.18, 0.19 (59)
(b) Neuropsychological evaluation				
Processing speed[c]	0.13, 0.33 (60)	–0.02, 0.86 (60)	0.09, 0.50 (60)	–0.06, 0.65 (58)
Verbal memory[d]	0.01, 0.96 (60)	–0.06, 0.66 (60)	–0.05, 0.69 (60)	–0.26, 0.05 (58)
Visuospatial memory[e]	–0.06, 0.66 (60)	0.08, 0.54 (60)	–0.02, 0.91 (60)	**–0.30, 0.02 (58)**
Fatigue[f]	–0.24, 0.08 (59)	–0.07, 0.63 (59)	–0.24, 0.07 (59)	0.02, 0.86 (59)
Depression score[g]	**–0.29, 0.03 (59)**	–0.23, 0.08 (59)	**–0.39, < 0.01 (59)**	–0.12, 0.40 (59)
(c) Global imaging parameters				
Intracranial volume	**0.80, < 0.01 (61)**	0.06, 0.67 (61)	**0.79, < 0.01 (61)**	**0.28, 0.04 (59)**
Cortical surface area	–	–0.14, 0.30 (61)	**0.82, < 0.01 (61)**	**0.39, < 0.01 (59)**
Cortical thickness	–	–	**0.43, < 0.01 (61)**	–0.27, 0.05 (59)
WM lesion volume	**0.39, < 0.01 (57)**	–0.23, 0.09 (57)	0.27, 0.05 (57)	–

[a]Bold results for $p < 0.05$.
[b]Neurological disability by EDSS.
[c]Processing speed by Symbol Digit Modalities Test.
[d]Verbal memory is sum score of the first five trials of the California Verbal Learning Test 2.
[e]Visuospatial memory is the sum score of the first three trials of the Brief Visuospatial Memory Test.
[f]Fatigue: mean of the Fatigue Severity Scale.
[g]Depression score is the sum score of the Beck Depression Inventory 2.
EDSS: Expanded Disability Status Scale; MRI: magnetic resonance imaging; n: number of patients in analyses; r: Pearson's correlation, controlled for age and gender; WM: white matter.

positively associated with WM lesion load ($r = 0.39$; $p < 0.01$) (Table 3). The association between depression score and surface area was still significant after controlling for WM lesion load ($r = -0.30$; $p = 0.03$). Mean cortical thickness was related to gender (patients: $r = 0.33$; $p = 0.01$ and controls: $r = 0.29$; $p = 0.02$), age (patients: $r = -0.40$; $p < 0.01$ and controls: $r = -0.70$; $p < 0.01$) and cortical volume (patients: $r = 0.33$; $p < 0.01$ and controls: $r = 0.35$; $p < 0.01$), but not with any clinical outcome measures (Table 3).

Comparison of regional cortical structure between patients and controls

We found no significant vertex-wise differences in cortical surface area between the patients and controls (Figure 2(a)); however, there were widespread differences in cortical thickness between the groups (Figure 2(b), Table 4(a), Table 4(b)). We found bilateral thickness differences in the pre- and post-central regions and large parts of the parietal lobe, as well as in the superior temporal and lateral occipital regions. There were also large regions of thickness differences in the superior frontal regions of the left hemisphere (Figure 2(b)). We found volume differences mainly in the same regions, most notably the pre- and post-central and in the superior parietal regions, bilaterally, and in the superior and orbital frontal regions of the left hemisphere (Figure 2(c), Table 4(a), Table 4(b)). The cerebral cortex of the patients was 5–5.5% thinner than that of the healthy controls, in the regions of significant thickness difference (Table 4(c)).

Associations between regional cortical structure and clinical symptoms within the patient group

We identified large confluent areas where smaller cortical surface area and volume were significantly associated with depressive symptoms, finding Pearson correlations mainly between $r = -0.25$ and $r = -0.50$ (Figure 3). The regions where reduced surface area related to depressive symptoms spanned the surface of the frontal pole, pars orbitalis and the orbital frontal; the rostral and caudal middle frontal and the pre- and post-central regions bilaterally in addition to the middle temporal, fusiform and parahippocampal regions of the left hemisphere (Figure 3(a)).

We saw the volume associations to depressive symptoms in most of the same regions: In the orbital frontal and pars orbitalis, the superior frontal, rostral and caudal middle

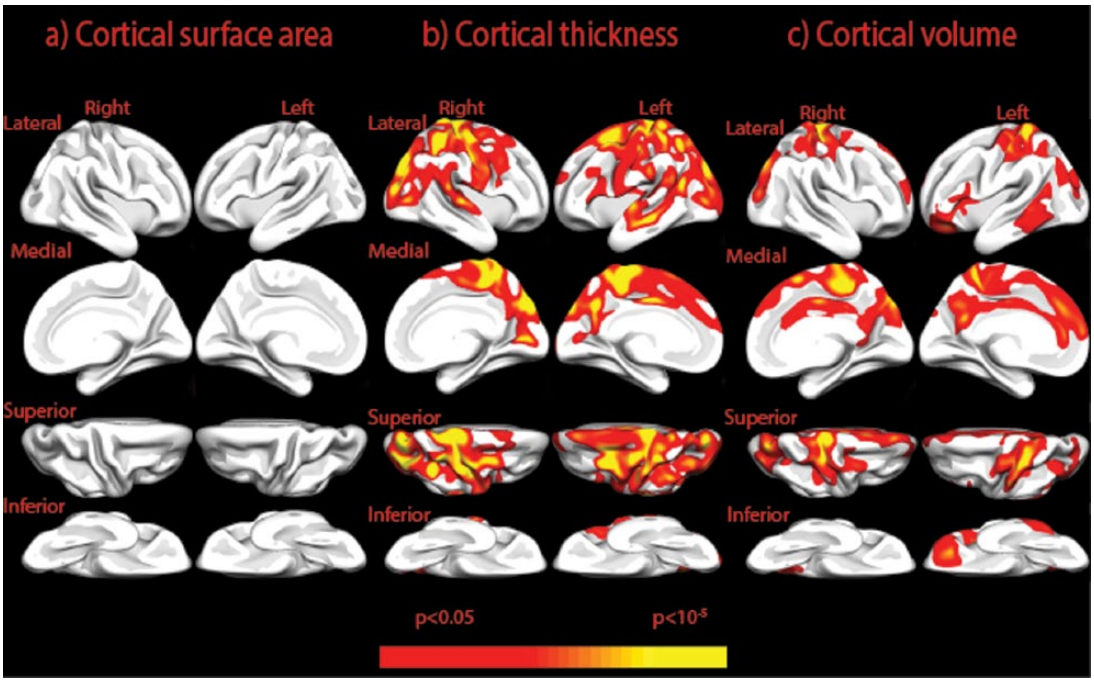


Figure 2. Differences in cortical structure between patients and controls.
The regions of significant differences between the groups of RRMS patients ($n = 61$) and controls ($n = 61$) were mapped on standard semi-inflated templates; depicted in lateral, medial, superior and inferior views, for the right and left hemispheres. The colored regions illustrate: (a) smaller cortical surface area, (b) thinner cortices and (c) smaller cortical volume, in the patients than in the controls. The colored bar illustrates the significance level of the differences, in red ($p < 0.05$) and yellow ($p < 10^{-5}$). The results were corrected for multiple comparisons by Monte Carlo simulations, and only the vertexes belonging to clusters surviving this correction are shown. RRMS: relapsing–remitting multiple sclerosis. Please go to:http://msj.sagepub.com/ for colour plates.

frontal, pre- and post-central of both hemispheres in the right supramarginal and superior temporal regions of the right hemisphere and in the fusiform and inferior temporal region of the left hemisphere (Figure 3(b)).

We further identified a region where thinner cortices were associated with neurological disability in the left lateral occipital, inferior parietal and inferior temporal region of the left hemisphere, and a corresponding volume effect in the left lateral occipital region (Figure 4(a)).

Processing speed was not associated with cortical structure in this sample, but we found that verbal memory was positively related to a larger cortical surface area in the lateral occipital, fusiform and inferior temporal region of the left hemisphere (Figure 4(b)) and that visuospatial memory was positively related to a larger cortical volume in the supramarginal and superior temporal region of the right hemisphere (Figure 4(c)).

Increased levels of fatigue were associated with smaller cortical volumes in the rostral and caudal middle frontal, and in parts of the pre- and post-central regions, of the right hemisphere of the MS patients (Figure 4(d)).

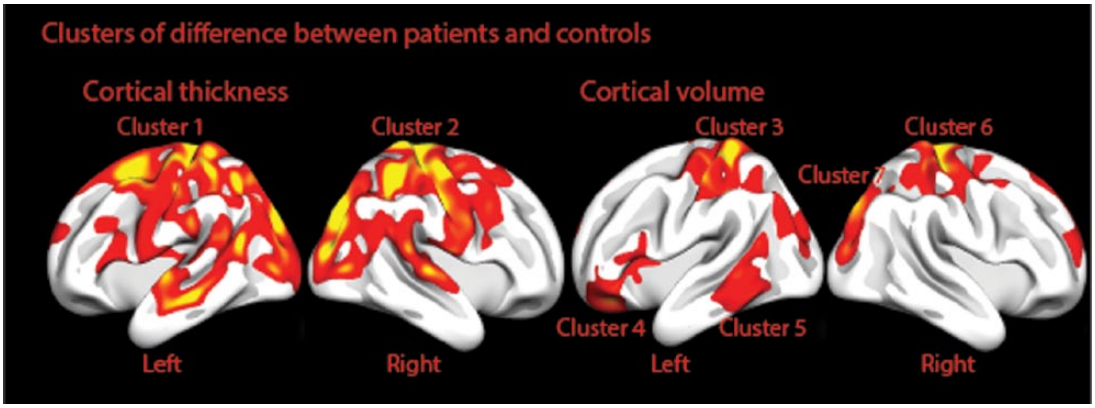
Discussion

In this population-based sample of 61 early RRMS patients and carefully matched healthy controls, we found a pronounced difference in cerebral cortical thickness, followed by several regions of differences in cortical volume between the groups. We identified no differences in cortical surface area between the groups; however, we found several regional associations between cortical surface area and clinical symptoms, most pronounced with depressive symptoms.

No differences in cortical surface area between patients and controls were seen in our sample. To our knowledge, only one pilot study [22] had previously evaluated cortical surface area in MS, investigating the cortical surface area of only six RRMS and nine secondary progressive MS patients, with a mean disease duration of 11.8 years. They found significant differences in surface area between MS patients and healthy controls, utilizing 2-dimensional surface

Table 4. Regions of differences in cortical grey matter between RRMS patients and controls. (a) Clusters of cortical thickness difference are spread continuously over both hemispheres and hence, not divided into separate clusters. Regions of volume differences are divided into Clusters 3–7; (b) Details of anatomical localization of the clusters, MNI coordinates of the center of each cluster; (c) Size of the clusters, including differences in thickness or volume in the clusters, between RRMS patients and controls. Please go to:http://msj.sagepub.com/ for colour plates.

(a)



(b) Cluster localization	Brain hemisphere	MNI coordinates			Cortical regions		
		x	*y*	*z*			
Cluster 1	left	–10.8	–35.1	53.5	Superior frontal; pre-, para- and post-central; superior and inferior parietal; superior temporal; lateral occipital		
Cluster 2	right	24.3	–28.8	51.3	Pre-, para- and post-central; superior and inferior parietal; superior temporal; lateral occipital		
Cluster 3	left	–25.8	–36.0	55.5	Pre-, para- and post-central		
Cluster 4	left	–22.6	35.8	–10.6	Superior and orbital frontal		
Cluster 5	left	–58.6	–44.7	–2.9	Banks of the superior temporal sulcus		
Cluster 6	right	23.9	–28.3	50.9	Pre-, par-a and post-central		
Cluster 7	right	21.4	–82.6	40.8	Superior parietal		
(b) Cluster Size	Cluster size	Patients (n = 61)			Controls (n = 61)	Difference	
Cortical thickness	mm^2	mm (SD)			mm (SD)	mm	CI
Cluster 1	35086	2.361 (0.114)			2.499 (0.120)	0.138	0.096–0.179
Cluster 2	27707	2.240 (0.114)			2.382 (0.117)	0.142	0.100–0.183
Cortical volume	mm^2	mL(SD)			mL(SD)	mL	CI
Cluster 3	14907	19.109 (1.639)			21.234 (1.651)	2.124	1.534–2.714
Cluster 4	3267	5.533 (0.484)			6.014 (0.550)	0.481	0.295–0.667
Cluster 5	2541	5.072 (0.897)			5.682 (0.796)	0.610	0.306–0.914
Cluster 6	9350	10.803 (0.895)			11.994 (0.927)	1.191	0.865–1.518
Cluster 7	7062	9.675 (0.846)			10.789 (1.015)	1.114	0.779–1.449

MNI: Montreal National Institute; mm: millimeters; mL: milliliter; RRMS: relapsing–remitting multiple sclerosis.

area, central gyrus depth and central gyrus angle as measures of differences in cortical surface area. Both the methods of quantification of cortical surface areas, study size and disease duration differ from our study, which may all contribute to the difference in results.

The pattern of cortical thickness differences without affecting the cortical surface area early in the disease course resembles an effect found in early Parkinson's disease, where a larger cortical surface area is observed in patients than in controls, in spite of regional cortical thickness reductions.[9] Smaller

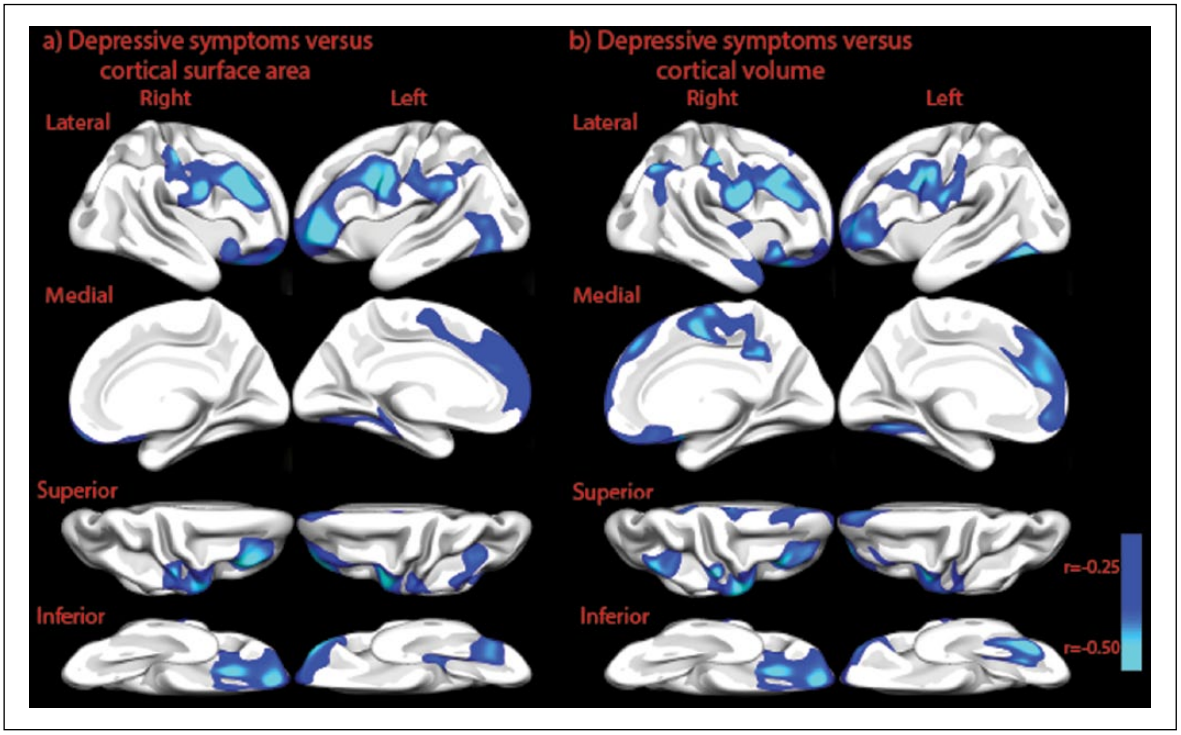


Figure 3. Associations between cortical structure and depressive symptoms within the patient group.
The regions of significant association between (a) cortical surface area and (b) cortical volume with the depressive symptoms in the patient group ($n = 59$) were mapped on standard semi-inflated templates; which are depicted here in lateral, medial, superior and inferior views for the right and left hemispheres, respectively. The colored regions illustrate a negative association with a significance level of $p < 0.05$, corrected for multiple comparisons by Monte Carlo simulations, and only the vertexes belonging to clusters surviving this correction are shown. The color bar illustrates the size of the Pearson correlation, controlled for age, gender and disease duration; with dark blue as $r = -0.25$ and light blue, $r = -0.50$. Please go to:http://msj.sagepub.com/ for colour plates.

cortical surface areas are identified in patients with Williams syndrome[23] and microcephaly.[24] Both a thinner cortex and a smaller cortical surface area is found in patients with schizophrenia, compared to healthy controls.[25] Patients with Alzheimer's dementia have cortical thickness reductions; one study did not find a reduction of surface area in the temporal lobe, compared to healthy controls.[8] Put together, these studies indicate that neurodevelopmental and neurodegenerative diseases affect the morphology of the cerebral cortex differently, and that cortical thickness reduction represents the primary change of cortical morphology in neurodegenerative diseases, as well as in MS.

We identified more widespread regional cortical thickness differences between early RRMS patients and healthy controls than most other studies, possibly both because of our study size and careful matching, and because of our unselected patient cohort. The first study of regional cortical thickness in MS[1] may not have identified all regions of cortical thickness differences between patients and controls, because of the small study sample. A recent multi-center study finds regional cortical thickness differences of a similar size as we found in our study, between RRMS patients and healthy controls in the frontal, parietal and temporal regions; but in contrast to our study, those patients were all part of a clinical trial, which may have resulted in a possible selection bias in that study.[3] Yet another study finds that thickness differences are larger and more widespread in patients with cognitive impairment, compared to cognitively normal patients.[4] As in another study of early MS patients,[5] our patient group consisted of both patients with a mild and a severe disease course; and may, therefore, be more representative of the early MS population as a whole.

In contrast to most other studies on cognition in early MS,[26] we did not identify cognitive decline in the domains of processing speed, verbal or visuospatial memory in our patient group. The number of patients identified as candidates for our study corresponds well with the incidence estimates in the region,[27] indicating that most of the recently-diagnosed patients in the region were identified in our study. The patients had

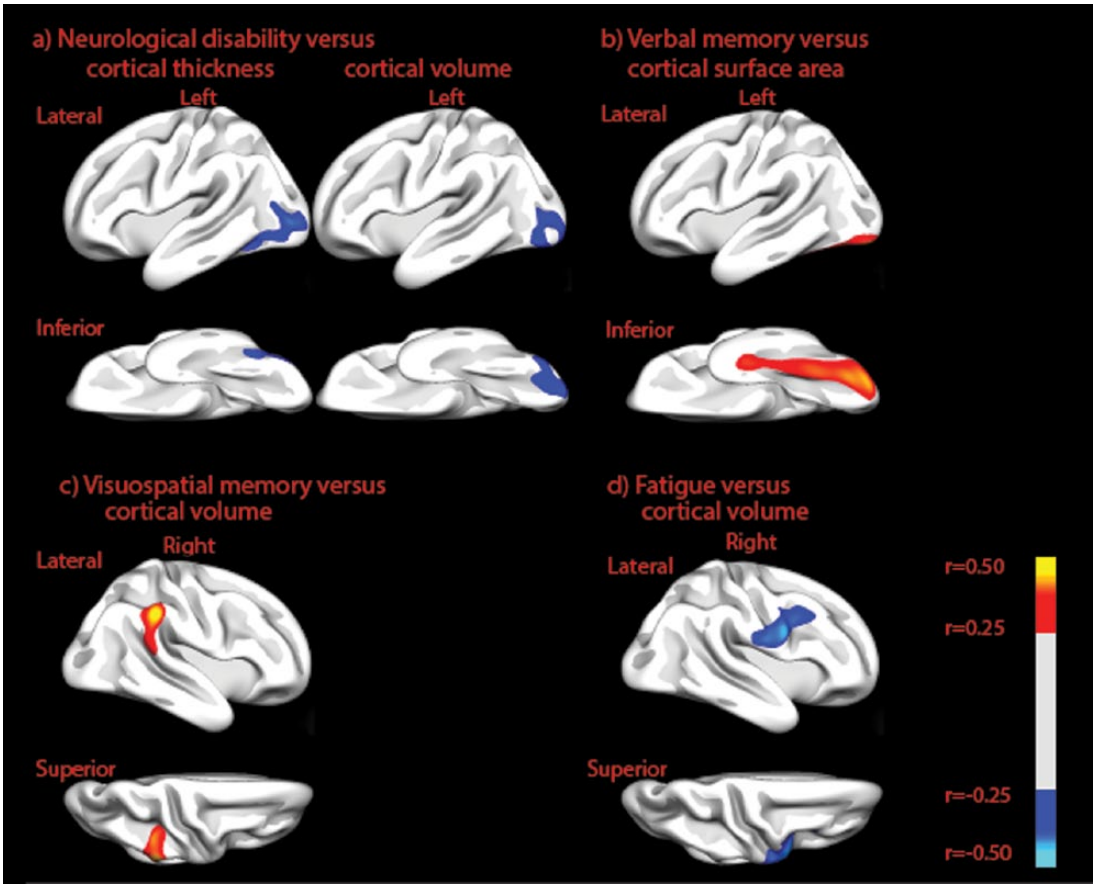


Figure 4. Associations between cortical structure and neurological disability, cognition and fatigue within the patient group. The regions of significant association between cortical surface area, thickness and volume and (a) neurological disability ($n = 61$), (b) verbal memory ($n = 60$), (c) visuospatial memory ($n = 60$) and (d) fatigue ($n = 59$) were mapped on standard semi-inflated templates, depicted here in lateral, medial, superior and inferior views for the right and left hemispheres. Only the views that add information to the reader were included in the figure. The colors indicate the direction of the association: Red/yellow regions indicate there was a positive association, while blue regions indicate there was a negative association. The colored regions illustrate regions of significant association ($p < 0.05$), corrected for multiple comparisons by Monte Carlo simulations: Only vertexes belonging to clusters surviving this correction are shown. The color bar illustrates the size of the Pearson correlation, controlled for age, gender and disease duration; with dark blue showing $r = -0.25$ and light blue $r = -0.5$ for the negative associations, and red showing $r = 0.25$ and yellow $r = 0.5$, for the positive associations. Please go to:http://msj.sagepub.com/ for colour plates.

high general ability levels and high levels of education; and most of the patients were either students or working, confirming that this is a well-functioning patient group. The combination of large regional thickness differences between patients and controls, as well as the sparse associations between cognitive performance and cortical morphology in our patient sample, fits with the cognitive reserve hypothesis[28] (i.e. that premorbid intelligence quotient (IQ) moderates or delays the negative effects of brain atrophy on cognition, in MS patients). It must, however, be kept in mind that the tests applied here do not capture all aspects of cognition that may be affected by the disease.

We identified a negative association between depressive symptoms and cortical surface area, mainly in the frontal and parietal lobes, which was also reflected in smaller cortical volume estimates in the same regions. Associations between depression and the frontal and parietal cortex were previously found.[29,30] Interestingly, the regions that were associated with higher depression scores in our group of patients did not overlap with the regions with average thickness or volume differences, between patients and controls. Cortical surface area was *positively* related to WM lesion load, possibly as a result of the mass effect that WM lesions may have early in the disease; however, the negative association between cortical surface area and depression did also hold, when controlling for WM lesion load. Our results indicated that some patients may have a structural susceptibility to depression and supported the growing evidence that

depression in MS is related to structural brain characteristics.[31]

A thalamo-striato-cortical determinant to fatigue in MS has been suggested in recent studies, and our results regarding fatigue are in line with other studies comparing GM characteristics between MS patients, with and without fatigue.[30,32,33] Our combined results support the concept that fatigue in MS is related, at least in part, to characteristics of frontal and parietal cortical areas, known to be involved in cognitive and attention processing, even from the early stages of disease.

Even in the absence of cognitive decline, we found that a better visuospatial memory in our patient group was associated with a larger volume in the supramarginal and superior temporal regions of the right hemisphere. Another study utilizing exactly the same visuospatial test found a significant association between test results and temporal lobe atrophy in MS patients.[34] Our results indicated that the cortical structural correlates of this test may be localized to the parietotemporal junction. Furthermore, we only found associations in the non-dominant hemisphere, known to be involved in non-verbal memory tasks.[35]

We found that a better verbal memory was associated with a larger surface area of the inferior temporal lobe of the dominant hemisphere. Functional studies of healthy individuals find activation of the right temporal lobe during memory encoding.[35] As the cortical surface area was unaffected in our patient sample, the structural associations identified may be caused by premorbid differences within the patient group, nevertheless our results supported that this commonly-used test for verbal memory in MS patients has a regional structural correlate.

Our study had several limitations. First, this is a cross-sectional comparative study, and even though we aimed at minimizing differences between the two groups by careful characterization and matching, we cannot rule out a selection bias. Second, our research protocol was set up to study morphological differences between RRMS patients and healthy controls. It did not include specific sequences suitable for detection of GM lesions, such as Double Inversion Recovery.

In conclusion, we found that the main differences in cortical structure between recently-diagnosed RRMS patients and healthy controls constitute widespread regional thickness differences. Cortical surface area appeared unaffected at this stage of the disease, but may still play a significant clinical role, as it was associated with cognition and depressive symptoms within our patient group. Future studies of cortical morphology in MS and other neurological diseases should differentiate between cortical surface area, cortical thickness and cortical volume. Longitudinal studies are warranted for investigations of the dynamic interplay between cortical structure and disease progression, and to identify the role of these changes in clinical manifestations of the disease.

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Conflict of interest

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