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Longitudinal Characterization of Cortical Lesion Development and Evolution in Multiple Sclerosis with 7.0-T MRI

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Conflicts of interest are listed at the end of this article.

See also the editorial by Filippi and Rocca in this issue.

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Background: Cortical lesions develop early in multiple sclerosis (MS) and play a major role in disease progression. MRI at 7.0 T shows high sensitivity for detection of cortical lesions as well as better spatial resolution and signal-to-noise ratio compared with lower field strengths.

Purpose: To longitudinally characterize *(a)* the development and evolution of cortical lesions in multiple sclerosis across the cortical width, sulci, and gyri; *(b)* their relation with white matter lesion accrual; and *(c)* the contribution of 7.0-T cortical and white matter lesion load and cortical thickness to neurologic disability.

Materials and Methods: Twenty participants with relapsing-remitting MS and 13 with secondary progressive MS, along with 10 age-matched healthy controls, were prospectively recruited from 2010 to 2016 to acquire, in two imaging sessions (mean interval, 1.5 years), 7.0-T MRI T2*-weighted gradient-echo images ($0.33 \times 0.33 \times 1.0$ mm^3) for cortical and white matter lesion segmentation and 3.0-T T1-weighted images for cortical surface reconstruction and cortical thickness estimation. Cortical lesions were sampled through the cortex to quantify cortical lesion distribution. The Expanded Disability Status Scale (EDSS) was used to assess neurologic disability. Nonparametric statistics assessed differences between and within groups in MRI metrics of cortical and white matter lesion burden; regression analysis explored associations of disability with MRI metrics.

Results: Twenty-five of 31 (81%) participants developed new cortical lesions per year (intracortical, 1.3 ± 1.7 vs leukocortical, 0.7 ± 1.9; $P = .04$), surpassing white matter lesion accrual (cortical, 2.0 ± 2.8 vs white matter, 0.7 ± 0.6; $P = .01$). In contrast to white matter lesions, cortical lesion accrual was greater in participants with secondary progressive MS than with relapsing-remitting MS (3.6 lesions/year $\pm$ 4.2 vs 1.1 lesions/year $\pm$ 0.9, respectively; $P = .03$) and preferentially localized in sulci. Total cortical lesion volume independently predicted baseline EDSS ($\beta = 1.5$, $P < .001$) and EDSS changes at follow-up ($\beta = 0.5$, $P = .003$).

Conclusion: Cortical lesions predominantly develop intracortically and within sulci, suggesting an inflammatory cerebrospinal fluid–mediated lesion pathogenesis. Cortical lesion accumulation was prominent at 7.0 T and independently predicted neurologic disability progression.

Online supplemental material is available for this article.

Multiple sclerosis (MS) is the leading cause of nontraumatic neurologic disability in young adults in Western countries. Cortical lesions play a major role in MS disease progression (1–3). The mechanisms involved in cortical lesion pathogenesis in MS, however, are still largely unknown. Neuropathologic evidence suggests that compartmentalized immune cell infiltration within the subarachnoid space represents a main component of cortical lesion pathology in both early (4) and progressive (1,5–8) MS stages. Cortical demyelination has also been found to strongly correlate with a specific inflammatory profile within the cerebrospinal fluid (CSF) (9). It has been suggested that immune cells within the meninges may foster subpial demyelination via soluble factors acting directly or indirectly through the activation of microglia. Since CSF flow within the subarachnoid compartment is likely to be restricted in the cerebral sulci, this could promote a preferential accumulation of cortical demyelination at these sites. The role of meningeal inflammation in cortical lesion progression, however, is still unknown, as some neuropathologic examinations have not observed an association between the two processes (10).

Abbreviations

CI = confidence interval, CSF = cerebrospinal fluid, DMT = disease-modifying therapies, EDSS = Expanded Disability Status Scale, MS = multiple sclerosis

Summary

Longitudinal 7.0-T MRI in multiple sclerosis demonstrates that the accrual rate of cortical lesions predominates over white matter lesion accumulation. Lesions preferentially occur intracortically and within cortical sulci and are associated with disability progression.

Key Points

- In patients with multiple sclerosis, 7.0-T MRI detects cortical lesions (higher for intracortical than leukocortical lesion type [1.3 ± 1.7 vs 0.7 ± 1.9, respectively; $P = .04$]) more frequently compared with previous studies at lower-field MRI strength, and shows no relationship with the rate of white matter lesion accumulation.
- Cortical lesions preferentially develop in cortical sulci, indicating a possible link with an ongoing cerebrospinal fluid–mediated neuroinflammatory process.
- Assessment of cortical lesions should represent a main component in the evaluation of progression of disease burden in multiple sclerosis.

In vivo visualization of cortical lesions at MRI allows tracking of lesion appearance and evolution over time. Longitudinal studies at lower field strength have provided relevant information on the rate of cortical lesion accrual in MS and their clinical correlates (11–14), although limited data on the spatial distribution of cortical lesion development and evolution within the cortical width or across sulci and gyri (15,16).

Ultra high–field-strength 7.0-T MRI combined with multichannel radiofrequency technology allows a substantial improvement in image signal-to-noise ratio and spatial resolution over 3.0-T systems (17), with increased cortical lesion detection rate (18,19).

Cross-sectional 7.0-T studies (20,21) have demonstrated abnormally increased quantitative T2* throughout the cortex of MS patients, with a greater distribution in sulci than in gyri. If decreased CSF flow in sulci plays a role in cortical lesion development, these would be the areas where cortical lesions would first appear.

We used T2*-weighted gradient-echo imaging at 7.0-T to assess longitudinally, in a heterogeneous MS cohort, the development and evolution of cortical lesions and their relationship with white matter lesion accumulation also derived from 7.0-T data. Furthermore, by quantitatively assessing the spatial distribution of cortical lesions within the cortex, we investigated whether cortical lesions preferentially develop within sulci. Finally, we assessed the relative contribution of cortical and white matter lesion load as seen on 7.0-T images and cortical atrophy to changes in neurologic disability.

Materials and Methods

Study Participants

This study, approved by an institutional ethics committee, recruited participants between 2010 and 2016. Written informed consent and Health Insurance Portability and Accountability Act approval were obtained from all participants. Thirty-three participants meeting the criteria for MS diagnosis (22), with either relapsing-remitting MS ($n = 20$) or secondary progressive MS ($n = 13$) (23), who met the inclusion or exclusion criteria (Fig 1), along with 10 age-matched healthy control participants, were prospectively enrolled in the study. Eighteen out of 31 participants had taken part in four previous studies (20,21,24,25) which assessed cortical lesions cross-sectionally. Two participants' data were discarded due to motion artifacts. Neurologic disability was quantified by certified neurologists (J.A.S. and R.P.K., with 18 and 32 years of experience, respectively) by using the Expanded Disability Status Scale (EDSS) (26) within a week from MRI. Disability progression was defined as sustained (3 months without relapse) higher EDSS of at least 1.0 point when the baseline EDSS was less than 6, or at least 0.5 points when the baseline EDSS was at least 6.

MRI Protocol and Image Analysis

Over a mean ± standard deviation of 1.5 years ± 0.5, study participants underwent two imaging sessions within a week on a 7.0-T and a 3.0-T MRI scanner (investigational device and TrioTim, respectively; Siemens, Erlangen, Germany) using 32-channel head coils to acquire 7.0-T two-dimensional fast low-angle shot T2*-weighted spoiled gradient-echo images to cover the supratentorial brain (repetition time/echo time [TR/TE] = 1700/21.8 msec, 0.33 × 0.33 × 1 mm^3 resolution) for lesion segmentation; 3.0-T three-dimensional magnetization-prepared rapid acquisition with multiple gradient-echoes sequence (TR/inversion time (TI)/TE = 2530/1200 msec, 0.9 × 0.9 × 0.9 mm^3 resolution) for cortical surface reconstruction, coregistration with 7.0-T data, and cortical thickness measurement (FreeSurfer Software version 5.3.0, 2013, Boston, Mass, *http://surfer.nmr.mgh.harvard.edu*).

Lesions were segmented using Slicer (version 4.4.0, 2014, *http://www.slicer.org*). New lesions were identified on a lesion-by-lesion basis through agreement by active collaboration of one radiologist (C.A.T.) and one neurologist (C.M.), with 16 and 20 years of experience, respectively, in neuroimaging analysis. Using the same sequence protocol, including one to 11 participants from this study cohort, the reproducibility of cortical lesion quantification and the interrater agreement (kappa = 0.69) were previously evaluated (24,25). Cortical lesions extending for at least 3 voxels across two consecutive slices were classified as intracortical if subpial (2) or confined to the cortex, or leukocortical if they also involved the white matter (Fig 2). Counts and volumes were quantified using FreeSurfer and FMRIB Software Library (FSL, version 5.0.11, 2017, Oxford, UK, *http://fsl.fmrib.ox.ac.uk*). Longitudinal lesion metrics were annualized to account for differences in follow-up duration by dividing new lesion count and volume to follow-up interval in each patient.

Pial and white matter surfaces and cortical thickness maps were generated using Freesurfer and lesion in-painting method. Leukocortical and intracortical lesion masks at each time point were projected on each subject's cortical surface, and the resulting two-dimensional lesion masks were normalized to a common surface template in FreeSurfer and averaged to obtain

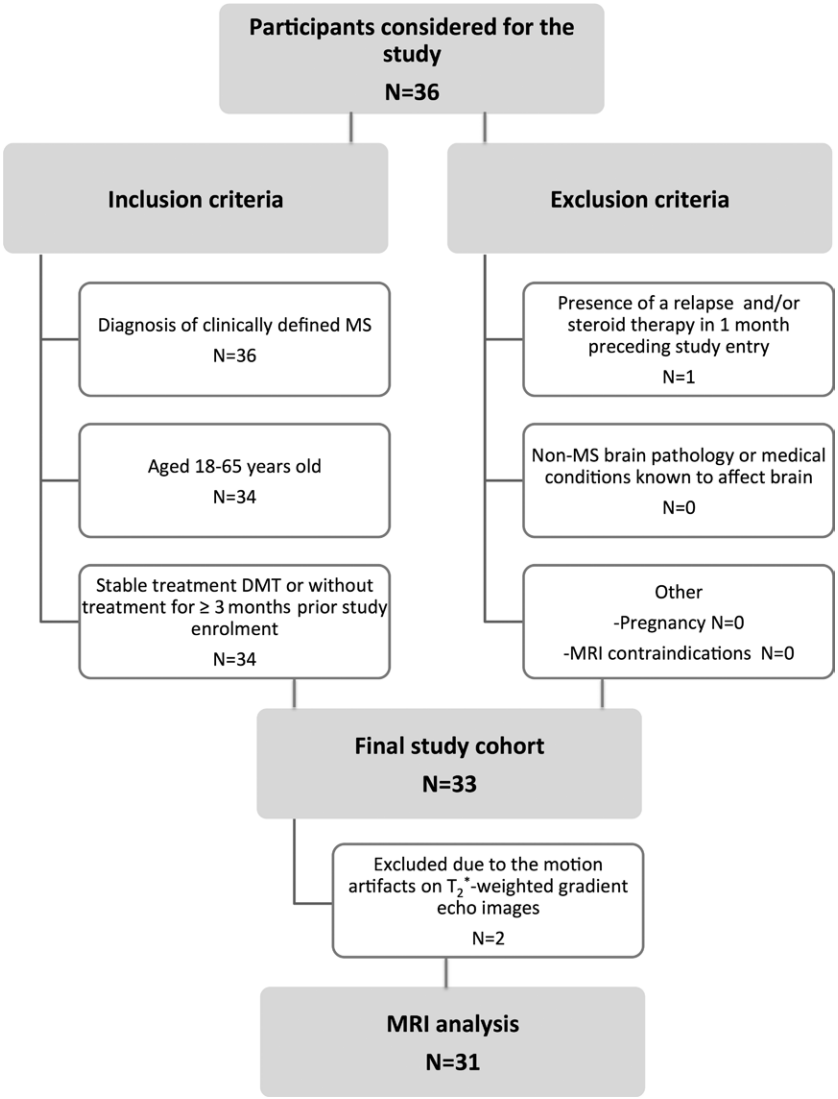

Figure 1: Flowchart shows inclusion and exclusion criteria. *DMT* = disease-modifying therapies, *MS* = multiple sclerosis.

distribution probability maps. Lesion probability peaks were localized by using the Desikan-Killiany atlas (27). The designation of the total cortical lesion surface area belonging to sulci and gyri was obtained in each patient by using the cortex curvature map based on the negative and positive values displayed by gyri and sulci, respectively (28).

The positive and negative values reflect how each vertex on the surface is distant from a hypothetical "mid-surface" that exists between the sulci and the gyri, in other words, how "deep" and how "high" are the brain folds. In FreeSurfer, this hypothetical surface is chosen so the mean of all the displacements is zero (*https://surfer.nmr.mgh.harvard.edu/fswiki*). In each patient, the mean cortical lesion (total and subtypes) surface area (mm^2) located in sulci and gyri was quantified by using Freesurfer at baseline and follow-up. The percentage of the cortical lesion sulcal surface area in the entire MS cohort, in relapsing-remitting MS and secondary progressive MS, was obtained by dividing the mean cortical lesion area in sulci by the mean total surface area (sulci plus gyri) in each group of interest.

Statistical Analysis

Demographic and/or imaging metrics were compared between groups (ie, patient vs controls, relapsing-remitting MS vs secondary progressive MS, and among treatment-based groups) by using the Mann-Whitney *U* test and Kruskal-Wallis test as appropriate and the Fisher exact test for sex and treatment repartition. Comparisons of MRI metrics within groups were estimated by the Student *t* test and Wilcoxon signed-rank test.

Univariable correlations between baseline MRI metrics and *(a)* baseline EDSS and *(b)* EDSS change were evaluated by using Spearman's rank correlation coefficient.

After EDSS ranking and logarithmical transformation of discrete variables, contributions of baseline variables (ie, white matter and cortical lesion counts or volumes, mean cortical thickness) to baseline EDSS and EDSS change were assessed by using stepwise linear regression. Significant variables retained in the models were evaluated for independence from white matter damage and cortical thickness by partial correlation. The Benjamini-Hochberg method (29) was applied to adjust for multiple comparisons when comparing MRI measures of lesion load within and across MS groups, after which *P* values less than .05 were indicative of statistical significance.

Statistical analysis was performed by using SPSS version 24 (IBM, Armonk, NY; M.P.S., with 20 years of experience).

Results

Demographic and clinical data of all participants are shown in Table 1. Age, disease duration, and EDSS were higher in secondary progressive MS relative to relapsing-remitting MS. All participants were either on stable treatment with disease-modifying therapies (DMT) or without any treatment for at least 3 months prior to study enrollment. Twenty-two percent (seven of 31) of participants (two with relapsing-remitting MS and five with secondary progressive MS), all on DMT, experienced EDSS progression at follow-up.

Intracortical and Leukocortical Lesion Pathology at Baseline

The MRI metrics of lesion load are given in Table 2. All participants had at least one cortical lesion (either intracortical or leukocortical) at baseline. Intracortical lesions were found in 15 of 20 participants with relapsing-remitting MS and in 10 of 11 participants with secondary progressive MS. Leukocortical lesions were present in 13 of 20 participants with relapsing-remitting MS and in all participants with secondary progressive MS. Participants with second-

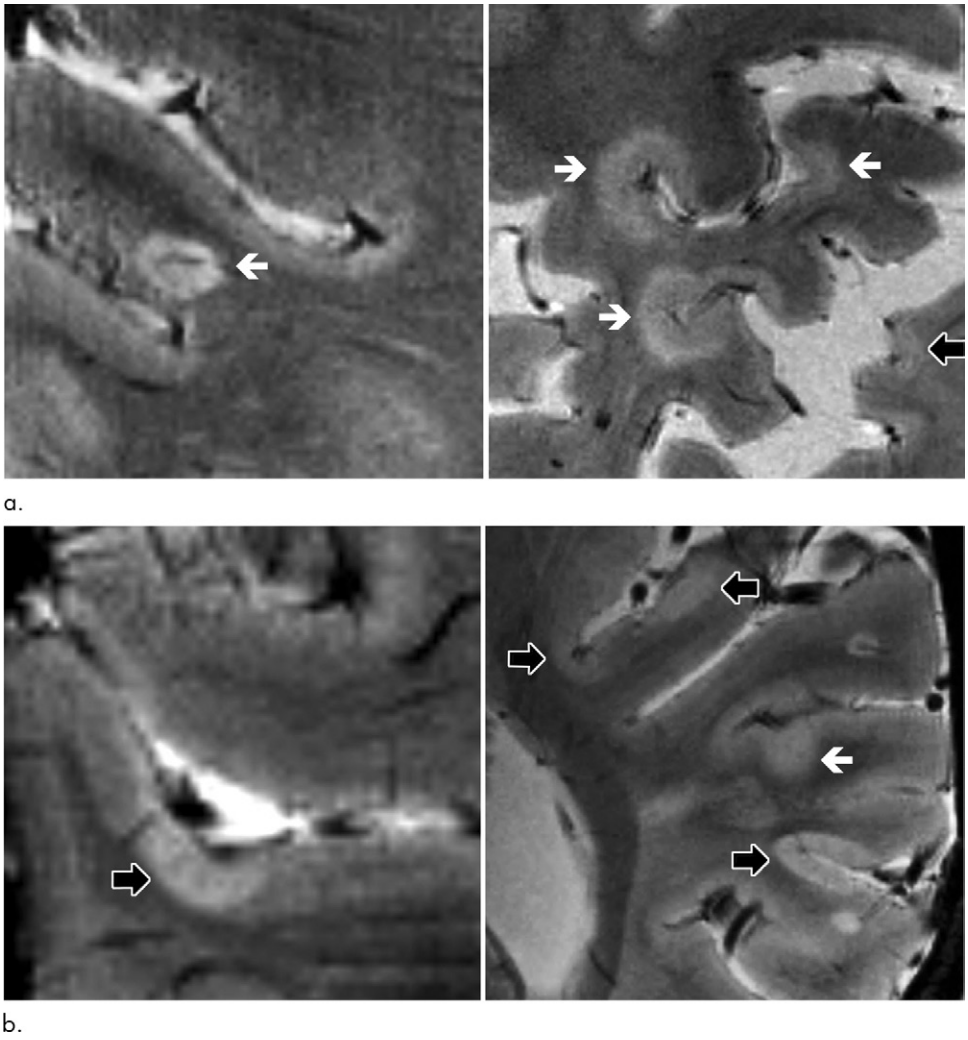

Figure 2: Axial 7.0-T T2*-weighted images show examples of leukocortical lesions (white arrows) and intracortical lesions (black arrows) along with juxtacortical and periventricular white matter lesions in different patients with multiple sclerosis (MS). **(a)** Images of two different brain locations in a 59-year-old man with secondary progressive MS (SPMS). **(b)** Images of two different brain locations in a 40-year-old woman with SPMS.

ary progressive MS had higher cortical and white matter lesion counts and volumes compared to participants with relapsing-remitting MS, though there were large individual differences (Table 2).

As shown by probability maps (Fig 3), cortical lesions were highly dispersed across the brain lobes. Intracortical lesions presented only a slight preference for the insular, superior temporal, and parietal cortices, while the highest distribution of leukocortical lesions was observed in superior frontal, caudal middle-frontal, precentral, and supramarginal areas (Fig 3). Despite the scattered distribution across cortical regions, cortical lesions were predominantly identified in cortical sulci (Table 3) in relapsing-remitting MS and, to a lesser extent, in secondary progressive MS. Looking at cortical lesion subtypes, leukocortical lesions demonstrated a similar distribution pattern while intracortical lesions predominated in cortical sulci in all disease stages.

No cortical lesions were found in healthy control participants, but white matter lesions (n = 21) were found in five of them.

New Cortical Lesions Predominantly Develop Intracortically and within Cortical Sulci

All cortical lesions detected at baseline remained visible at follow-up. Twenty-five out of 31 participants (81%) had at least one new cortical lesion (Fig 4), either intracortical or leukocortical. Altogether, 93 new cortical lesions were identified in 25 participants (30 cortical lesions in relapsing-remitting MS and 63 in secondary progressive MS).

The annual cortical lesion accumulation rate was higher in the group of participants with secondary progressive MS versus the group with relapsing-remitting MS (mean ± SD, 3.6 lesions/year ± 4.2 vs 1.1 lesions/year ± 0.9, respectively; corrected P = .03, Mann-Whitney U test, [Table 2]). Altogether, the annual accumulation rate and volume were greater for the intracortical than for the leukocortical lesion subtype (accumulation rate [mean ± SD], 1.3 lesions/year ± 1.7 vs 0.7 lesions/year ± 1.9, respectively [corrected P = .04]; volume, 59 mm^3/year ± 90 vs 11 mm^3/year ± 32, respectively [corrected P = .003], by Wilcoxon signed rank test for related samples). Intracortical lesion volume was also greater at follow-up (mean ± SD, 651 mm^3 ± 891 vs 498 mm^3 ± 682; corrected P = .006, Wilcoxon signed rank test for related samples) while leukocortical lesion volume did not change significantly (P = .25).

New cortical lesions (both intracortical and leukocortical) were preferentially distributed in cortical sulci rather than in gyri, even if the gyri were also involved (Table 3). The highest percentage of the total surface area filled by new cortical lesions located in the sulci was observed in participants with relapsing-remitting MS.

At follow-up, the preferential distribution of cortical lesions in cortical sulci observed at baseline persisted in the entire MS cohort, although it decreased slightly (Table 3).

No significant difference was found in cortical lesion load between participants with either first- or second-line DMT and those without therapy throughout the study duration (Table E1 [online], P = .21–.99).

Table 1: Demographics and Clinical Characteristics of Study Participants

Characteristic	Controls (n = 10)	P Value*	RRMS (n = 20)	SPMS (n = 11)	P Value†
Sex‡		.06			.32
Male	6		4	4	
Female	4		16	7	
Age at baseline (y)§	39.9 ± 0.5 (30–56)	.69	41.3 ± 10.5 (22–51)	39.9 ± 8.5 (23–63)	.02
Disease duration (y)§	—	—	6.0 ± 6.2 (1–21)	19.9 ± 9.0 (10–40)	<.001
Follow-up interval (y)§	1.7 ± 0.5 (0.9–2.9)	.23	1.3 ± 0.2 (0.8–1.9)	1.6 ± 0.8 (1–3.9)	.15
Baseline EDSS‖	—	—	2.0; 0.9 (1–4)	5.0; 2 (2–6.5)	<.001
Follow-up EDSS‖	—	—	2.0; 1.3 (1–4)	6.0; 2.5 (3.5–6.5)	<.001
Therapy‡	—	—	16	10	.63
Interferon beta-1a			5	3	
Glatiramer acetate			3	3	
Dimethyl fumarate			4	3	
Fingolimod			1	—	
Natalizumab			3	—	
Cyclophosphamide			—	1	

Note.—EDSS = Expanded Disability Status Scale, RRMS = relapsing-remitting multiple sclerosis, SPMS = secondary progressive multiple sclerosis.

* For comparisons between all patients and healthy controls.

† For comparisons between RRMS vs SPMS groups.

‡ Data are numbers of participants.

§ Data are means ± standard deviation. Data in parentheses are ranges.

‖ Data are medians; interquartile range. Data in parentheses are ranges.

Table 2: MRI Metrics of Cortical and White Matter Lesion Load at Baseline and Follow-up in 31 Subjects with Multiple Sclerosis

Parameter	Multiple Sclerosis (n = 31)	Relapsing-Remitting MS (n = 20)	Secondary Progressive MS (n = 11)	P Value*
Baseline				
Count				
Total cortical	6; 27 (1–172)	5; 6.7 (1–33)	32; 119 (6–172)	<.005
Intracortical	6; 8 (0–48)	3.5; 5.7 (0–22)	11; 23 (0–48)	.008
Leukocortical	3; 9 (0–144)	1; 3 (0–26)	27; 92 (3–144)	<.005
White matter	34; 73 (6–227)	20; 26 (5–140)	78; 171 (34–227)	<.005
Volume (mm^3)				
Total cortical	584; 1735 (10–10736)	203; 570 (10–1897)	2320; 6865 (584–10763)	<.005
Intracortical	177; 453 (0–2737)	122; 415 (0–1269)	472; 1543 (0–2737)	.02
Leukocortical	196; 639 (0–9052)	91; 269 (0–1547)	1737; 6565 (196–9052)	<.005
White matter	1509; 5694 (120–31460)	452; 1378 (120–7116)	7695; 15386 (1509–31460)	<.005
Follow-up				
Count (lesions/y)				
Total cortical	1.1; 1.7 (0–12.5)	0.8; 1.7 (0–3.6)	2.3; 3 (0–12.5)	.03
Intracortical	0.8; 1.8 (0–8.9)	0.7; 1.4 (0–2.7)	1; 2.2 (0–8.9)	.07
Leukocortical	0; 0 (0–6)	0; 0 (0–3.6)	0; 3.3 (0–6)	.36
White matter	0.6; 0.8 (0–2.2)	0.7; 0.7 (0–2.2)	0; 0.6 (0–0.8)	.01
Volume (mm^3/y)				
Total cortical	43.8; 67.3 (0–439)	40 ; 70 (0–127)	46; 187 (0–439)	.38
Intracortical	35.6; 52 (0–439)	37; 62 (0–121)	34; 89 (0–439)	.75
Leukocortical	0; 0 (0–166)	0; 0 (0–64)	0; 20 (0–166)	.36
White matter	4.9; 13.1 (0–172)	9; 13 (0–172)	0; 5 (0–17)	.02

Note.—Data are medians; interquartile ranges. Data in parentheses are ranges. All P values are corrected for multiple comparisons using false discovery rate. MS = multiple sclerosis.

* For comparisons between the group of participants with relapsing-remitting MS vs the group of participants with secondary progressive MS.

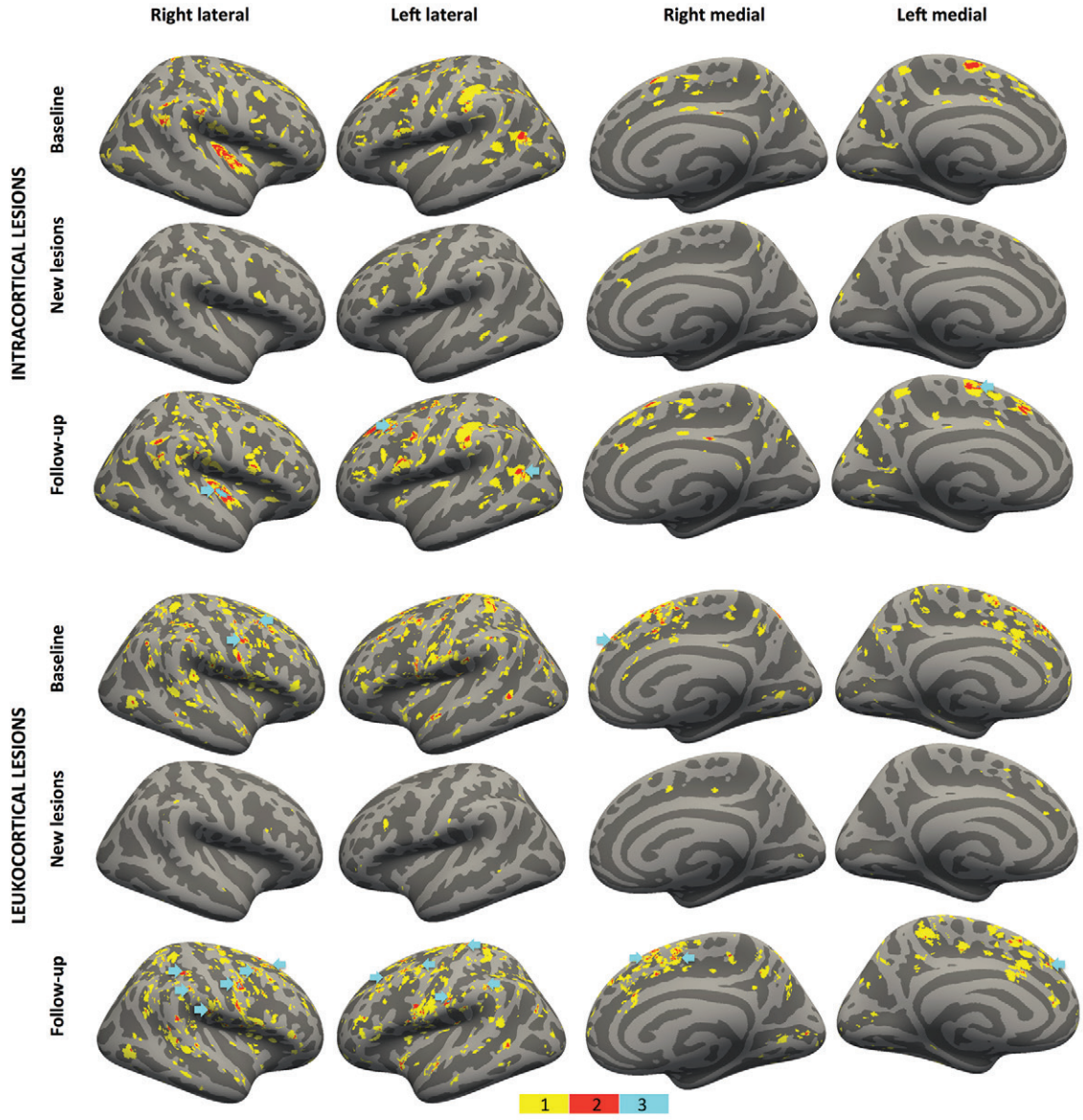

Figure 3: Spatial distribution of vertex-wise frequency of intracortical and leukocortical lesions in 31 patients with multiple sclerosis at baseline and at follow-up. The lesion frequency is displayed for every voxel in the color overlay on "fsaverage." The number of patients showing cortical lesions in a particular voxel is specified by the bar. Maximum overlap (arrows) corresponds to lesions in 10% (three of 31) of patients. Despite the scattered distribution, cortical lesions are mainly confined within cortical sulci (shown as dark gray areas) while cortical gyri (shown as light gray areas) are less involved.

No cortical lesions developed in healthy control participants at follow-up.

Lack of Correlation between Cortical and White Matter Lesion Accumulation

During follow-up, a total of 29 new white matter lesions (24 in the group of participants with relapsing-remitting MS and five in the group with secondary progressive MS) appeared in 68% (21 of 31) of participants. The annual accumulation rate of white matter lesions was higher in participants with relapsing-remitting MS than in those with secondary progressive MS (mean ± SD, 0.8 ± 0.6 vs 0.3 ± 0.3, respectively; corrected P = .01, Mann-Whitney test). White matter lesion volume was higher at follow-up relative to baseline in both the relapsing-remitting MS and secondary progressive MS groups (Table 2), though statistical significance was reached only for participants with relapsing-remitting MS (mean ± SD, baseline vs follow-up: 1460 mm^3 ± 2127 vs 1658 mm^3 ± 2240, respectively; corrected P = .002 by Wilcoxon signed rank test for related samples). No correlation was found between the annual accumulation rate of cortical lesions and white matter lesions (P = .69 for counts). Overall, the annual lesion accumulation rate was higher in the cortex than in the white matter (2.0 lesions/year ± 2.8 vs 0.7 lesions/year ± 0.6, respectively; corrected P = .01 by Wilcoxon signed rank test for related samples).

Table 3: Cortical Lesion Proportion in Sulci in 31 Participants with Multiple Sclerosis

Lesion Type by Group	Baseline (%)	Follow-up (%)	New Lesions (%)
All multiple sclerosis (*n* = 31)			
Total cortical	65 (280/428)	64 (306/472)	75 (48/64)
Intracortical	74 (201/273)	73 (235/323)	78 (49/63)
Leukocortical	57 (425/749)	58 (443/765)	65 (43/66)
Relapsing-remitting MS (*n* = 20)			
Total cortical	73 (97/132)	73 (121/165)	76 (45/59)
Intracortical	75 (114/152)	75 (149/199)	75 (47/63)
Leukocortical	67 (62/92)	67 (60/90)	97 (31/32)
Secondary progressive MS (*n* = 11)			
Total cortical	61 (522/849)	63 (539/862)	67 (50/75)
Intracortical	73 (329/450)	72 (353/491)	71 (51/72)
Leukocortical	56 (821/1466)	57 (861/1502)	58 (48/83)

Note.—Data are reported as percentage of the cortical lesion surface area located in sulci. Data in parentheses are the average cortical lesion surface area (square millimeters) in sulci divided by the average total surface area (sulci plus gyri, square millimeters). MS = multiple sclerosis.

Although there was no significant difference in white matter lesion load between participants with or without therapy, both at baseline and follow-up (Table E1 [online], P = .06–0.84), we observed a higher annual accumulation rate of white matter lesion volume in untreated versus treated participants (P = .06, Kruskal-Wallis test).

No new white matter lesions appeared in healthy control participants.

Cortical Gray Matter Atrophy

We did not observe any significant cortical thinning over the follow-up period in either the MS cohort (mean cortical thickness, 2.39 mm ± 0.10 at baseline vs 2.38 mm ± 0.95 at follow-up; P = .30) or in the healthy control participants (mean cortical thickness, 2.49 mm ± 0.9 at baseline vs 2.49 mm ± 0.6 at follow-up; P = .61).

Cortical Lesions and Neurologic Disability

Table 4 shows correlations for the whole MS cohort between baseline metrics of cortical and white matter lesion load and cortical thickness with *(a)* baseline EDSS and *(b)* changes in EDSS over the study period. Cortical lesion count and volume (both for total and cortical lesion subtypes) positively correlated with baseline EDSS and EDSS change. Baseline EDSS, but not EDSS change, correlated positively with white matter lesion count and volume, and inversely with cortical thickness. Accrual of new cortical or white matter lesions was not associated with EDSS change. No correlation was found between changes in white matter volume or in cortical thickness and EDSS changes.

Stepwise regression analysis revealed that only total cortical lesion volume at baseline was an independent predictor both for baseline EDSS (β = 1.5; 95% confidence interval [CI]: 0.8, 2.1; $P < .001$; R^2 = 0.27) and EDSS change (β = 0.5; 95% CI: 0.2, 0.8; P = .003; R^2 = 0.23) (Fig 5). The correlations between total cortical lesion volume and EDSS, and between total cortical lesion volume and EDSS change, remained significant even after adjusting for baseline cortical thickness and white matter lesion volume (ρ = 0.46; 95% CI: 0.13, 0.70; P = .01) and for changes in white matter lesion volume and cortical thickness, respectively (ρ = 0.56; 95% CI: 0.26, 0.76; P = .002).

Discussion

In this study, using a quantitative approach that combines ultra high–resolution T2*-weighted gradient-echo acquisitions at 7.0-T with a surface-based analysis, we demonstrated that cortical lesions in MS preferentially develop intracortically and within the cerebral sulci and that their accumulation is overall independent from and superior to white matter lesion accrual. These findings indicate that cortical lesions are likely driven by inflammatory events occurring in cerebral sulci, which previous neuropathologic examinations have reported as a preferential site of meningeal inflammation and possible restricted CSF flow with consequent stagnation of inflammatory soluble mediators (6,8,30). Our results also show that cortical lesion volume at baseline is related to EDSS progression independently from white matter damage and cortical atrophy, highlighting the potential value of cortical lesion assessment at 7.0 T in the evaluation of progression of disease burden.

While we demonstrated that new cortical lesions develop mostly within the cortical ribbon and that the total surface area filled by new intracortical lesions is greater in the sulci than in the gyri in all disease stages, we found that the total surface area filled by intracortical lesions located in the sulci was slightly lower at follow-up relative to the baseline. This may indicate a decrease in the sulcal nonlesioned surface available for cortical lesion formation over time, as well as continuous evolution of cortical pathology with ongoing processes of demyelination, inflammation, remyelination, and spreading into cortical gyri (31).

Although preferentially located in cortical sulci, we found that cortical lesions were scattered across the cortex and showed only a slight preferential distribution for some areas, including the insula and temporal cortex, as previously reported in histopathologic findings (2,3). Frontal, sensorimotor, and parietal regions also seemed to be more commonly affected.

By direct comparison with histopathology specimens, it has been demonstrated that, regardless of the pulse sequence, the greatest sensitivity of 3.0-T MRI is for leukocortical lesions and that 7.0-T MRI detects more than twice as many cortical lesions compared with 3.0-T MRI (19). Although we did not directly compare 7.0-T MRI versus 3.0-T MRI in ability to detect and characterize cortical lesions in our MS cohort, we found that the annual cortical lesion accumulation rate at 7.0 T in our population was

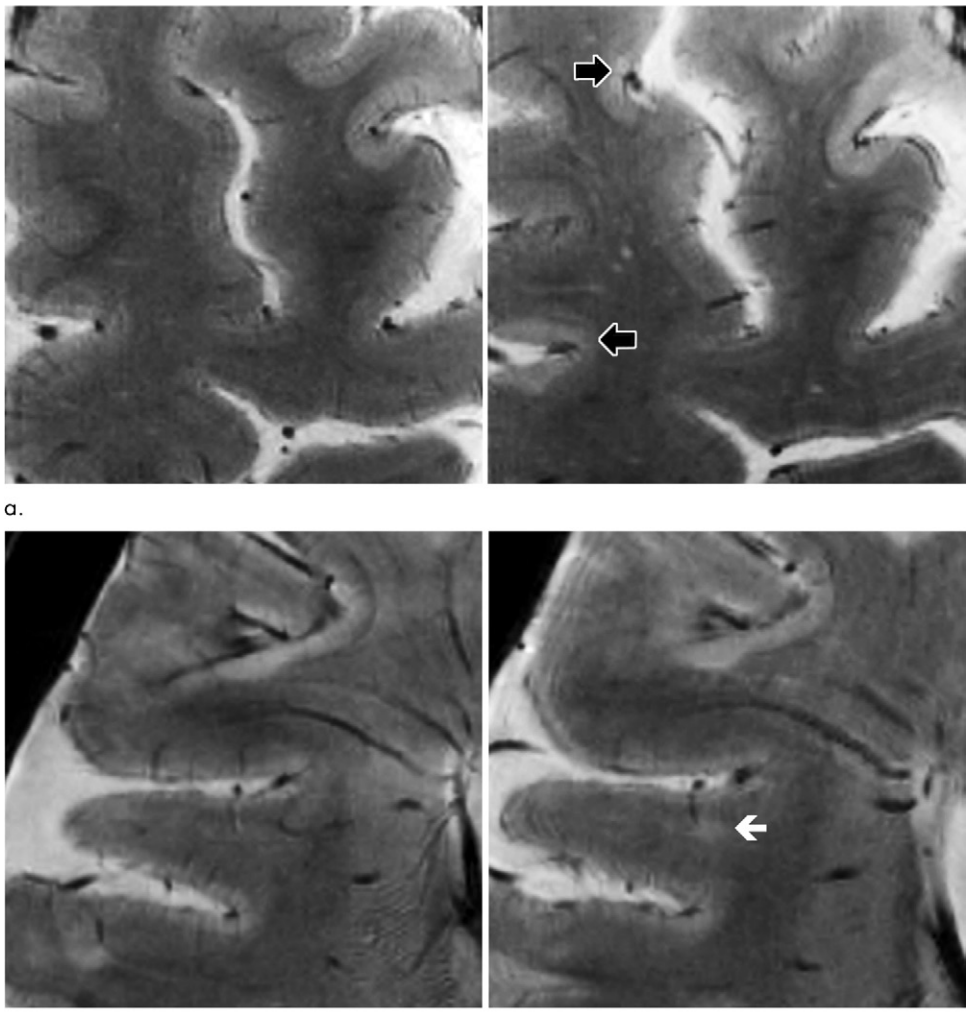

Figure 4: Axial high-resolution T2*-weighted images acquired at 7.0-T MRI. **(a)** Comparison of images at baseline (left panel) and 1.5-year follow-up (right panel) in a 52-year-old woman with secondary progressive multiple sclerosis (disease duration of 21 years) shows development of two intracortical lesions (black arrows) at follow-up. **(b)** Comparison of images at baseline (left panel) and 1.4-year follow-up (right panel) in a 43-year-old woman with relapsing-remitting multiple sclerosis (disease duration of 8 years) shows a new leukocortical lesion (white arrow) at follow-up.

approximately twice that reported by previous studies at lower field strength, which, similar to our study, included fairly typical MS cohorts (1.1 per patient per year in participants with relapsing-remitting MS and 3.6 per patient per year in participants with secondary progressive MS in our study vs 0.8 per patient per year in patients with relapsing-remitting MS and 1–1.6 per patient per year in patients with secondary progressive MS in previous studies) (13,16). We also found that the intracortical lesion subtype contributed to this rate to a greater extent than the leukocortical lesion subtype, suggesting that leukocortical lesions may require more time to develop.

In contrast to what was observed in the cortex, we found that the annual accumulation rate of white matter lesions at 7.0-T was relatively similar to that reported at 3.0-T (16), and, interestingly, significantly lower than and overall unrelated to cortical lesion progression. These observations strongly corroborate the notion that the development of white matter and cortical lesions in MS is likely independent.

Longitudinal studies at lower field strength (11,13), even if unable to detect intracortical subpial demyelination, have shown that the cumulative neurologic disability in MS is strongly associated with cortical pathology. We demonstrated that at 7.0-T, with an increased sensitivity for intracortical lesion detection, the total cortical lesion volume is the sole predictor of EDSS and is independent not only from white matter damage but also from cortical atrophy.

There are some limitations to our study: the relatively small size of our MS and healthy control cohorts, the lack of cognitive assessment that could have highlighted an association between cortical lesions and cognitive deterioration as observed by cross-sectional 7.0-T reports (14,32), the shorter follow-up period than in previous studies at lower field strength (13,16), which might account for the relatively limited dynamics in

Table 4: Correlations between MRI Characteristics (Baseline) and Neurologic Disability for the Study Cohort

Characteristic	Baseline EDSS (ρ)	EDSS Change (ρ)
Lesion type		
Total cortical		
Count	0.59	0.50
Volume	0.70	0.51
Intracortical		
Count	0.41	0.48
Volume	0.42	0.48
Leukocortical		
Count	0.71	0.40
Volume	0.73	0.36
White matter		
Count	0.51	NS
Volume	0.61	NS
Cortical thickness	−0.41	NS

Note.—Rho (ρ) derived by Spearman rank correlation analysis. EDSS = Expanded Disability Status Scale, NS = not significant.

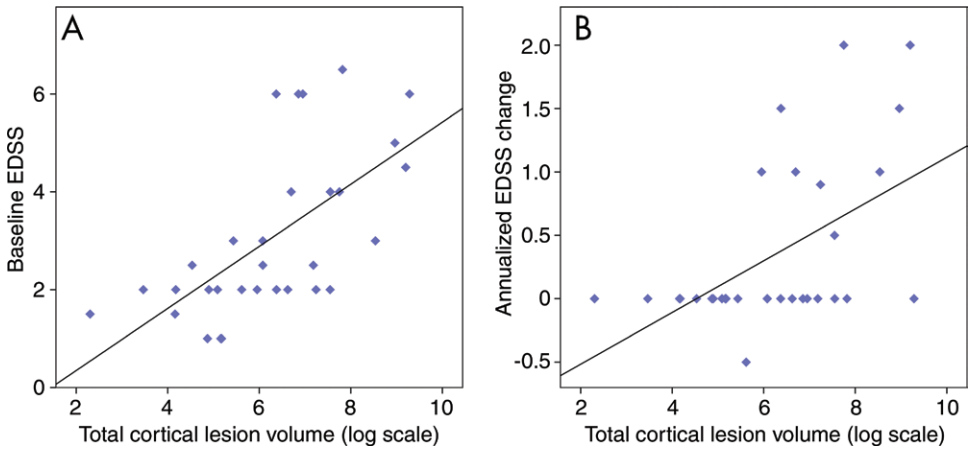

Figure 5: Scatter plots showing the univariable association between baseline total cortical lesion volume and, *A*, baseline EDSS and, *B*, EDSS change. Stepwise regression analysis shows that baseline total cortical lesion volume was retained as the only independent predictor of baseline EDSS score ($P < .001$, $R^2 = 0.27$) and EDSS changes at follow-up ($P = .003$, $R^2 = 0.23$). *EDSS* = Expanded Disability Status Scale.

EDSS observed across the entire cohort. Cortical lesion accumulation rate at 7.0 T, however, was revealed to be significant, even within such a short time period of observation. We also did not assess the contribution of spinal cord lesions to neurologic disability, though initial 7.0-T data suggest that, when both spinal cord and cortical MRI metrics are considered, cortical pathology shows the greatest association with EDSS (33).

Since 7.0-T MRI still fails to detect a large number of intracortical lesions in MS (as proven by postmortem histopathologic examination) regardless of the sequence type (18,19,34), the development of new methods at ultra-high–field-strength MRI is warranted to investigate the clinical significance of different lesion types in different MS stages.

In conclusion, our study shows that the rate of cortical lesion accumulation in MS patients is higher at 7.0-T compared with previous studies at lower field strength. Given that this accumulation is associated with progression of neurologic disability, its quantification might represent a useful tool for improving the monitoring of disease burden evolution.

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