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Characterization of thalamic lesions and their correlates in multiple sclerosis by ultra-high field MRI

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Abstract

Background: Thalamic pathology is a marker for neurodegeneration and MS disease progression.

Objective: To 1) characterize the morphology of thalamic lesions, their relation to 2) cortical and white matter (WM) lesions and 3) clinical measures; 4) assess the imaging correlates of thalamic atrophy.

Methods: Ninety MS patients and 44 healthy controls, underwent acquisition of 7-Tesla images for lesion segmentation, 3-Tesla scans for atrophy evaluation. Thalamic lesions were classified according to shape and presence of a central venule. Regression analysis identified the predictors of 1) thalamic atrophy, 2) neurological disability and 3) information processing speed.

Results: Thalamic lesions were mostly ovoid than periventricular, and for the great majority (78%) displayed a central venule. Lesion volume in the thalamus, cortex, and WM did not correlate with each other. Thalamic atrophy was only associated with WM lesion volume ($p=0.002$). Subpial and WM lesion volume were associated with neurological disability ($p=0.016$; $p<0.001$); WM and thalamic lesion volumes related with cognitive impairment ($p<0.001$; $p=0.03$).

Conclusion: Thalamic lesions are unrelated to those in cortex and WM, suggesting that they may not share common pathogenic mechanisms, and do not contribute to thalamic atrophy. Combined WM, subpial and thalamic lesion volumes at 7-Tesla contribute to disease severity.

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Declaration of Conflicting Interests

All authors declare no potential conflicts of interest.

Keywords

multiple sclerosis; thalamus; atrophy; central venule; ovoid; periventricular

INTRODUCTION

Multiple sclerosis is a chronic demyelinating and neurodegenerative disease that affects both the gray and white matter (WM) of the CNS[1]. Previous pathologic and MRI studies have shown that gray matter (GM) pathology in MS is often an early phenomenon with significant correlation to clinical disability, cognition and disease progression[2–6]. The thalamus is an interconnected deep GM structure frequently affected in the course of MS. Thalamic abnormalities including focal demyelinating lesions, atrophy, and microstructural tissue changes appear early in the disease and contribute to neurological and cognitive impairment[7–9].

Local neuronal loss, demyelination, and axonal damage are frequently reported as the substrates of thalamic atrophy[10]. Morphological features of thalamic lesions, including shape and location, can also help explain the mechanisms underlying the pathogenesis of focal thalamic demyelination. It has been reported that thalamic lesions typically line the ventricular surface[11]. Lesions in proximity to the lateral ventricle may be influenced by the CSF and therefore more susceptible to inflammatory cells and mediators including activated microglia and macrophages[1,12]. Local inflammatory activity, characterized by cytotoxicity and axonal transection, can further drive axonal injury or loss with resulting neurodegeneration[12]. The thalamus is also particularly prone to pathological processes due to its interconnectivity with other brain structures and regions[13].

With its high prevalence, studies are supporting the notion that thalamic degeneration can be used as a predictor for disease evolution[7,14] and even serve as a biomarker for neurodegeneration in MS[10, 15]. Initial data at 7 Tesla (T) MRI of MS patients have indeed found a positive correlation between thalamic and cortical lesion volume, suggesting that thalamic lesion assessment may be an estimate of overall GM lesion burden in the disease[16]. Other studies, however, have reported that thalamic degeneration and atrophy are more closely related to WM pathology because of axonal transection in WM tracts[17, 18]. While ultra-high resolution 7T MRI demonstrates increased sensitivity and detection of cortical and thalamic lesion volume[19–21], the knowledge regarding thalamic involvement in MS at 7T mainly stems from small patient cohorts.

The main objective of this study was to take advantage of a relatively large MS cohort of 90 patients at different stages of the disease imaged at 7T to better characterize different aspects of thalamic pathology, assess to which extent those are linked to cortical and WM pathology and could be considered as a rapid estimate of overall brain gray matter disease burden in MS.

Specifically, we aimed to 1) characterize the morphology of thalamic lesions, their relation to 2) cortical and WM lesions and 3) clinical outcome measures; 4) to assess the imaging correlates of thalamic atrophy.

MATERIALS AND METHODS

Study participants

Our Institution Ethics Committee approved all study procedures and a written informed consent was signed by all participants enrolled in the study.

Ninety MS patients (61 RRMS, 29 SPMS) and 44 age-matched healthy controls were prospectively enrolled in the study between 2011–2016. Inclusion criteria for MS patients were: age between 18–60 years, ≥ 8 years of schooling, and stable treatment with disease-modifying agents for at least 3 months or no treatment. Exclusion criteria included a relapse in prior 3 months, and cortisone treatment in prior one month. Four patients' data were discarded due to the motion artifacts on 7T acquisitions.

Subjects underwent a clinical examination to assess neurological disability using the Expanded Disability Status Scale (EDSS), and information processing speed, a domain frequently and early affected in MS, using the Symbol Digit Modalities Test (SDMT). Standard Z-scores for this test were obtained based on age and education of each participant.

MRI protocol and image analysis

All participants underwent two scanning sessions within approximately a week on 7T and 3T scanners (Siemens, Germany) using a 32-channel phased array coil to acquire: a) 7T single-echo FLASH T_2*- weighted spoiled gradient-echo pulse sequence (resolution = 0.33 × 0.33 × 1 mm^3) for lesion segmentation at the cortical, WM, and thalamic levels; b) 3T 3D magnetization-rapid acquisition with multiple gradient echoes (resolution = 0.9 × 0.9 × 0.9 mm^3) T1-weighted structural image for cortical surface reconstruction using FreeSurfer (http://surfer.nmr.mgh.harvard.edu) with cortical thickness estimation, co- registration with 7T data. Thalamic volume was obtained using FSL-FIRST (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST) and normalized to total intracranial volume.

All topological defects in cortical surfaces were corrected by lesion inpainting method. Cortical, WM and thalamic lesions were segmented by consensus of two experienced raters using Slicer v4.2.0 (http://www.slicer.org). Cortical lesions that extended for at least three voxels across two consecutive slices were classified as 1) type I (leukocortical) lesions that extend across both WM and the cortical GM; 2) type II (intracortical) lesions located within the cerebral cortex; 3) type III and type IV (subpial) lesions, extending from pial surface to cortical layers 3 and 4 or through the entire width of the cortex but without involving subcortical WM (Figure 1). Lesion counts and volumes were quantified using FreeSurfer and FSL (version 5.0, http://fsl.fmrib.ox.ac.uk) tools.

Thalamic lesions subtypes were classified according to MRI appearance: ovoid lesions (small discrete ovoid areas) and periventricular lesions (diffuse lesions lining the periventricular surface)[17]. The presence of a central vein was acknowledged inside thalamic lesions according to the North American Imaging in Multiple Sclerosis Cooperative criteria[22] as follows: 1) could be visualized a single linear hypointensity/dot in at least two perpendicular planes 2) the vein must be located centrally regardless of the lesion shape.

STATISTICAL ANALYSIS

Statistical analysis was performed using JMP Pro v13 software. As a result of the data not being normally distributed, Spearman's rank correlation test was used for assessing bivariate correlations between thalamic and either cortical or WM lesion volumes. Regression analysis was used to quantify the association between thalamic volume and lesion volumes (WM lesions, cortical lesions and thalamic lesions) along with cortical thickness, age, and gender. The independent contribution of imaging metrics (thalamic volume, thalamic lesion volume, cortical lesion volume types, white matter lesion volume, and cortical thickness) to EDSS and SDMT scores were assessed by using stepwise linear regression. The models were adjusted for potential confounds, such as age and gender for EDSS score and only gender for SDMT (age was accounted for in the Z-score calculation and thus not included as a covariate).

The variables that were not normally distributed were logarithmically transformed while EDSS score was ranked before entering into the regression model. The regression models assumptions were checked using a residual versus fitted values plot. An alpha of 0.05 (two-tailed, equal variances not assumed) was considered statistically significant.

RESULTS

Lesion characteristics at 7T

Demographics and clinical data of study subjects are reported in Table 1.Thirty-eight out of 90 patients (42%) showed thalamic lesions (53% in RRMS and 47% in SPMS). Overall, SPMS patients had a higher thalamic lesion count and volume relative to RRMS patients, though there were large individual differences (mean±SD; count: 2.6±1.9 versus 1.3±0.7, $p = 0.01$; volume: 162.5±247.6 versus 42.3±45.8, $p = 0.01$ by Mann-Whitney U-test).

Seventy-two thalamic lesions were identified in the MS cohort. Ovoid lesion were more prevalent than the periventricular lesions (Figure 2) both in the entire cohort (mean±SD; 1.6±1.4 versus 0.3±0.5, $p < 0.001$, by related samples Wilcoxon signed rank test) and in each disease phenotype (mean±SD; RRMS: 1±0.6 versus 0.3±0.6, $p < 0.001$; SPMS: 2.3±1.7 versus 0.2±0.4, $p < 0.001$, by related samples Wilcoxon signed rank test). The mean volume of ovoid lesions was smaller than periventricular lesions (mean±SD; 73.7 ± 99.4 mm^3 versus 133.2 ± 186.5 mm^3, $p = 0.295$, by related samples Wilcoxon signed rank test, Table 2).

Amongst MS patients with thalamic lesions, 28/38 (74%) of them displayed only lesions with a central venule, 6/38 (16%) of patients only lesions without a central venule, 4/38 (10%) both lesions with and without a central venule. In each disease phenotype, lesions harboring a central venule predominated (RRMS: 16/20 [80%]; SPMS: 16/18 [89%]).

Cortical lesions were identified in 88/90 (98%) of patients. Fifty-nine out of 61 (97%) RRMS patients had at least one cortical lesion while all SPMS patients presented with cortical lesions (Table 3). Thirty-six out of 38 (95%) patients with thalamic lesions also displayed cortical lesions. Interestingly, patients with thalamic lesions had on average, a

higher cortical lesion load both in terms of counts and volume (cortical lesion counts: 31.7 vs. 9.8, $p < 0.001$; cortical lesion volume: 2361.5 mm^3 vs. 590.2 mm^3, $p < 0.001$, by Mann-Whitney U Test) than patients with no evidence of thalamic lesions. However, in the same group comparison, only WM lesion count was higher in patients with thalamic lesions (71.3 vs. 41.8, $p = 0.011$) whereas WM lesion volume did not differ. No lesions were identified in healthy controls.

Correlates of thalamic lesion volume

We were not able to find any correlations between individual thalamic (total, ovoid, periventricular, venular, non-venular) and cortical (total, intracortical, leukocortical) lesion subtypes (P-values ranged from 0.14 to 0.97).

Also, no correlations were found between overall thalamic lesion volume and WM lesion volume. Interestingly, a mild correlation was found between thalamic venular lesion volume and WM lesion volume (rho = 0.4, $p = 0.02$).

Thalamic atrophy relates with white matter lesion volume

MS patients had a lower mean normalized thalamic volume of compared to healthy controls ($6.1 \cdot 10^{-3} \pm 1.1 \cdot 10^{-3}$ vs $6.8 \cdot 10^{-3} \pm 1 \cdot 10^{-3}$ mm^3, $p = 0.001$ by linear regression, adjusting for age and gender). This finding was confirmed in the MS subgroups including RRMS ($6.5 \cdot 10^{-3} \pm 7.4 \cdot 10^{-4}$ mm^3; $p = 0.003$) and SPMS ($5.4 \cdot 10^{-3} \pm 9.8 \cdot 10^{-4}$ mm^3; $p < 0.001$) (Table 5).

We were not able to find any differences in thalamic volume between groups of patients with or without thalamic lesions ($p = 0.198$) (Table 4).

Univariate correlations showed that normalized thalamic volume was inversely associated with thalamic (rho = −0.2, $p = 0.02$), WM (rho = −0.6, $p < 0.001$), and cortical lesion volume (rho = −0.4, $p < 0.00$), and was related to cortical thinning (rho = 0.4, $p < 0.001$).

Multivariate regression analysis results demonstrated that thalamic atrophy in MS patients had a strong association with WM lesion volume ($p = 0.002$, $R^2 = 0.24$), unrelated to cortical thickness ($p = 0.77$) and both thalamic ($p = 0.24$) and cortical lesion volume ($p = 0.63$) (Figure 3, Table 5). Age and gender were included as adjustment variables. Model residuals had a normal distribution.

Outcomes of clinical metric associations

In MS subjects, the independent contribution of imaging metrics to EDSS and SDMT was assessed by stepwise regression models. We found that after adjusting for age, gender, and cortical thickness, WM lesion volume (B = 17.2 [95% CI: 10.4, 24.1]; $p < 0.001$) and subpial cortical lesion volume (B = 5.2 [95% CI: 1.0, 9.4]; $p = 0.016$, R^2=0.36) were associated with a higher EDSS score. Impairment in SDMT was significantly associated with WM (B = −1 [95% CI: −1.4, −0.6]; $p < 0.001$) and thalamic lesion volume (B = −0.4 [95% CI: −0.7, −0.05]; $p = 0.03$, R^2=0.29).

DISCUSSION

In this study, using 7T MRI in a large cohort of MS patients, we found that WM lesion volume was associated with thalamic atrophy. Furthermore, our findings demonstrate that thalamic atrophy in MS patients is not related with either thalamic or cortical lesion volume. We also observed that the prevalence of thalamic lesions (46%) is lower compared to cortical lesions (98%). However, no association was detected between thalamic and cortical lesion volume. In the thalamus, ovoid morphology was more prominent than the periventricular type and frequently overlapped with the presence of a central venule. Our results also show that EDSS relates to WM and subpial cortical lesion volume independently from thalamic damage and cortical atrophy. Instead, lower SDMT z-scores were associated with an increase in both thalamic and WM lesion burden.

With 7T T_2* susceptibility imaging, there is a greater ability to characterize distinct thalamic lesion patterns that could be used in future studies for better understanding thalamic pathology in MS. The presence of a central venule could underlie a distinct pathological process, where lesion morphology is influenced by location and orientation of the veins[23]. This could provide further evidence that demyelination in focal thalamic lesions is perivascular and that venular anatomy may influence lesion morphology[24]. “Dawson’s finger” has been used as a model to represent the direction of demyelination in WM because it points in the direction of the vessel which correlates with the shape of the lesion[25]. It could also indicate the presence of inflammatory activity within the perivenular space of the lesion[26]. These findings suggest that ovoid lesions are determined by vascularity since there were abundantly more central veins in that type of lesion compared to periventricular. Furthermore, we found a correlation between thalamic venular lesion volume and WM lesion volume, cluing towards common pathologic source.

However, despite the high sensitivity for central vein detection demonstrated by 7T MRI[27], in our study, not all ovoid lesions were centered by a venule. This could be related to weak visualization of the internal lesion morphology due to a reduced lesion/venule size. Alternatively, it can also indicate a type of lesion that is linked more to Wallerian degeneration/axonal loss[11] from distal WM lesions than to local inflammation.

In contrast, periventricular thalamic pathology may be more susceptible to demyelination and interaction with factors produced by adjacent CSF due to the proximity of the thalamus to the ventricles[17]. Studies provide also evidence that subpial cortical pathology is influenced by cytotoxic factors in meningeal inflammation[28, 29]. Despite this, we were not able to identify a relationship between periventricular thalamic lesions and subpial lesions, but however, we are underpowered for such an analysis since we identified periventricular thalamic lesions only in a reduced number of patients (8).

Contrary to previous 7T imaging findings[16], we did not find a correlation between thalamic lesions and cortical lesions, although patients with thalamic lesions had overall increased WM and cortical lesion burden. Our study included a larger MS cohort, and differences in the type of sequence and resolution used for cortical lesion detection may also account for the disparities with previous 7T data. Given the high prevalence of cortical lesions as

opposed to thalamic lesions and the fact that the thalamus is a smaller GM structure compared to the cortex, a strong association between the two measures might not necessarily be expected.

We also investigated the relationships between thalamic, cortical, and WM lesions to determine the role of local and distant pathological processes in inducing thalamic atrophy. Using ultra-high field MRI, which shows increased sensitivity to thalamic and cortical lesion pathology, we found that thalamic lesions are not as frequent as cortical lesions. While cortical lesions were detected in almost all subjects (98%), thalamic lesions were identified in less than half of the cohort. All but two patients with thalamic lesions also presented with cortical lesions.

Consistent with previous studies, we found that thalamic atrophy was greater in all disease stages relative to healthy controls[1,7, 8, 10, 12, 14, 15, 17, 18, 30, 31]. However, pathological processes underlying neurodegeneration in the thalamus are still uncertain. Our data indicated that thalamic atrophy in MS is not associated with local T_2* lesion formation or distant cortical lesion formation. The lack of association between thalamic focal lesions and thalamic volume is consistent with prior findings[31]. Instead, we found a strong association between WM lesion volume and thalamic atrophy, in line with previous reports[32]. Taken together, these results suggest that Wallerian degeneration from distant WM lesions and disconnection mechanisms, might play a greater role than local thalamic lesions in inducing thalamic atrophy in MS. Due to the thalamus' interconnectivity with cortical areas and other brain structures, and evidence that thalamic atrophy develops from the earliest disease stages, a better understanding of the substrates of thalamic demyelination and neurodegeneration is critical to improving our understanding on the pathogenesis of MS.

Future longitudinal studies are needed for better understanding the processes leading to thalamic atrophy and how these can be used as predictors of disease burden, or even if they vary according to age or disease phenotype. Also, considering the fact that WM lesions harboring a paramagnetic rim have been associated with a poor prognosis[33, 34] it will be valuable to determine if the paramagnetic rim is present also at the thalamic level and how it relates with overall lesion load, stage or disease aggressiveness.

Finally, we used stepwise regression models to quantify the association between thalamic lesion volume, thalamic atrophy together with heterogeneous MRI metrics and clinical outcome measures. Our findings are consistent with previous reports in highlighting the contribution of cortical subpial lesion type to physical disability[28, 35, 36] since the retained predictors of EDSS increase were only cortical subpial and WM lesion volume. Our data also suggest that WM and thalamic lesion volume account for the 29% of the variance in cognitive performance. Given that the thalamic axons transmit information between subcortical and specific cortical areas it is not surprisingly that the thalamic nuclei/connections damage are clinically translate into cognitive disability[37, 38].

CONCLUSIONS

Our study showed that ovoid lesions were more prevalent than periventricular lesions in the thalamus and venular lesions were more common than non-venular lesions. The data demonstrated that thalamic lesion volume is not related to overall cortical lesion volume including intracortical and leukocortical lesions, thereby suggesting either that thalamic and cortical lesion pathology may not share common pathogenic mechanisms or that may develop at different rates. Furthermore, thalamic atrophy is independent from thalamic and cortical lesion volume. Instead, WM lesion volume serves as better predictor for thalamic neurodegeneration. The combined metrics of WM, subpial and thalamic lesion volumes acquired at 7T explain disease severity.

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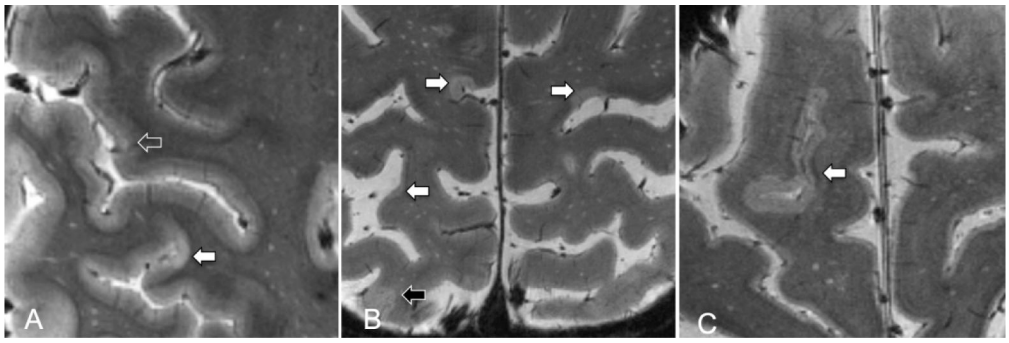

Figure 1. Examples of cortical lesion subtypes on 7 Tesla T_2*-weighted MRI images.

(A-C) Images show examples of multiple MS lesions (white arrows showing subpial lesions; open arrow showing type 2 intracortical lesion; black arrow showing leukocortical lesion)

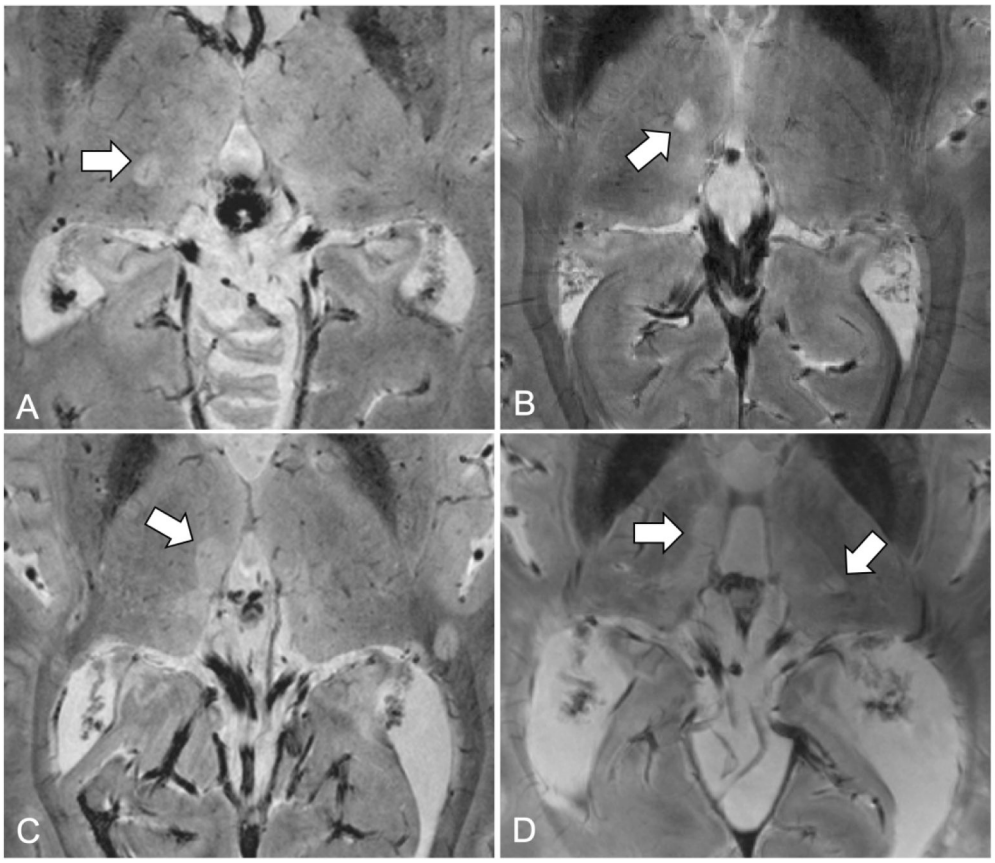

Figure 2. Examples of thalamic multiple sclerosis lesions on 7 Tesla T_2*-weighted MRI images.
(A) Ovoid lesion with central venule on right thalamus; (B) Ovoid lesion without central venule on right thalamus; (C) Periventricular lesion on third ventricle; (D) Multiple thalamic lesions including periventricular and ovoid lesions.

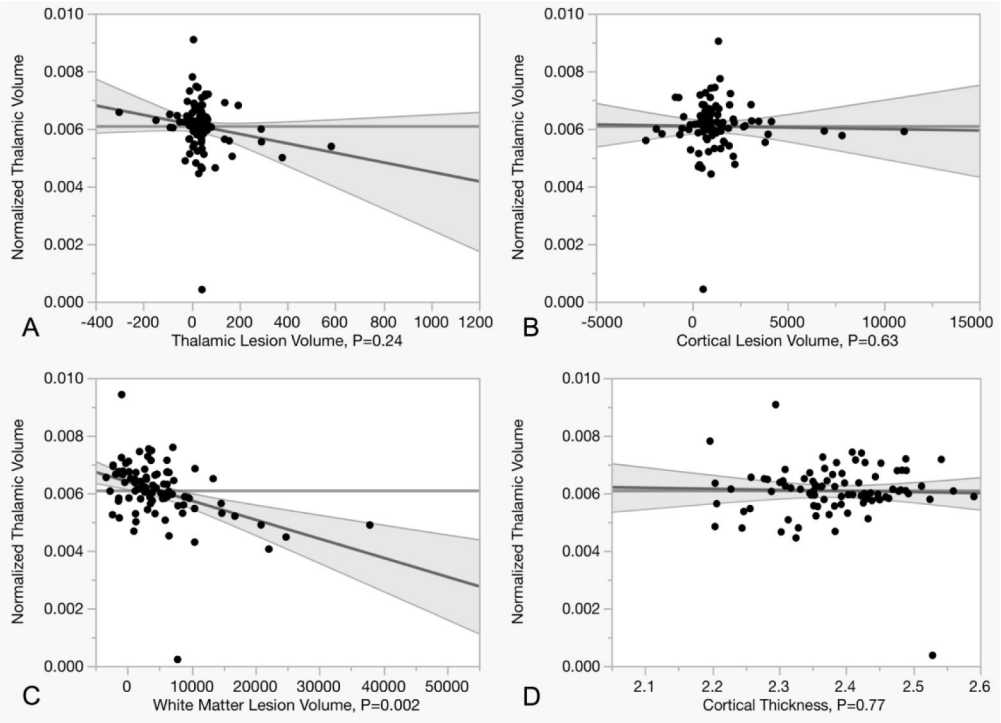

Figure 3. Relationship between normalized mean thalamic volume and MRI metrics at 7 Tesla and 3 Tesla.

Scatter plots summarizing the relationship between thalamic volume and thalamic (A), cortical (B), and white matter (C) lesion load at 7T as well as with cortical thickness (D). The multivariate regression shows how thalamic volume correlates with white matter lesion load, but not with cortical thickness and thalamic or cortical lesion load.

Table 1.

Demographic, clinical, and MRI characteristics of study subjects with thalamic lesions.

	All	RRMS	SPMS
N	90	61	29
Gender (M/F)	23/67	13/48	10/19
Age, years	42.3 (9.2)	40 (8.6)	47.1 (8.7)
Disease duration, years	9.1 (9.2)	5.2 (5.7)	17.6 (9.6)
EDSS score, median (range)	2.5 (8)	2.1 (1.1)	4.5 (6)
SDMT, Z-score	−0.04 (1.5)	0.5 (1.1)	−1.3 (1.4)
Education	15.9 (2.7)	16.2 (2.8)	15.2 (2.5)
Caucasian: African American: Asian	87:2:1	59:2:0	28:0:1
Therapy			
Dimethyl Fumarate	18	14	4
Natalizumab	16	12	4
Glatiramer Acetate	18	12	6
Interferon Beta-1a	16	10	6
Cyclophosphamide	1	0	1
Monoclonal Antibody	2	0	2
Immunosuppressant	1	1	0
No Treatment	18	12	6

Abbreviations: RRMS = relapsing remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; EDSS = Expanded Disability Status Scale; All values are reported as mean (SD) if not as otherwise noted

Table 2.

Counts and volumes of lesions in thalamus.

	All (N = 38)	RRMS (N = 20)	SPMS (N = 18)	p-value*
Total Thalamic Lesions				
Count	1.9 ± 1.5	1.3 ± 0.7	2.6 ± 1.9	**0.006**
Volume, mm^3	99 ± 182	42 ± 46	163 ± 248	**0.01**
Ovoid Lesions				
Count	1.6 ± 1.4	1 ± 0.6	2.3 ± 1.7	**0.002**
Volume, mm^3	74 ± 99	32 ± 28	113 ± 125	**0.003**
Number of subjects	35	17	18	
Periventricular Lesions				
Count	0.3 ± 0.5	0.3 ± 0.6	0.2 ± 0.4	0.797
Volume, mm^3	133 ± 187	62 ± 50	223 ± 265	0.678
Number of subjects	9	5	4	
Venular Lesions				
Count	1.5 ± 1.4	1 ± 0.6	2.1 ± 1.7	**0.021**
Volume, mm^3	63 ± 77	28 ± 24	97 ± 96	**0.006**
Number of subjects	32	16	16	
Non-venular Lesions				
Count	0.4 ± 0.9	0.4 ± 0.9	0.5 ± 0.8	0.343
Volume, mm^3	177 ± 301	100 ± 69	229 ± 391	0.208
Number of subjects	10	4	6	

Abbreviations: RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis;

*for comparisons between RRMS and SPMS subjects; all values are reported as mean ± SD

Table 3.

Counts and volumes of lesions in cortex and white matter.

	All (N = 90)	RRMS (N = 61)	SPMS (N = 29)	p-value*
Total Cortical Lesions				
Count	20.7 ± 31.3	10.3 ± 10.9	42.2 ± 46.3	**<0.001**
Volume, mm^3	1405 ± 2406	608 ± 871	2775 ± 3626	**<0.001**
Intracortical Lesions				
Count	9.4 ± 11.7	6.3 ± 7.9	14.9 ± 13.9	**0.003**
Volume, mm^3	477 ± 723	311 ± 514	824 ± 955	**0.008**
Type II Cortical Lesions				
Count	0.5 ± 1.0	0.5 ± 0.8	0.5 ± 1.2	0.522
Volume, mm^3	5.4 ± 11.8	5.2 ± 9.7	5.7 ± 15.5	0.610
Subpial Cortical Lesions				
Count	8.9 ± 11.5	5.9 ± 7.6	14.4 ± 13.6	**0.002**
Volume, mm^3	471 ± 722	306 ± 513	819 ± 954	**0.007**
Leukocortical Lesions				
Count	11.5 ± 24.8	4.0 ± 5.9	27.3 ± 38.4	**<0.001**
Volume, mm^3	705 ± 1489	276 ± 548	1606 ± 2271	**<0.001**
White Matter Lesions				
Count	54.2 ± 56.2	36.3 ± 34.9	90.4 ± 72.9	**<0.001**
Volume, mm^3	4884 ± 7925	2268 ± 2964	10386 ± 11600	**<0.001**

Abbreviations: RRMS = relapsing remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis;

*for comparisons between RRMS and SPMS subjects; all values are reported as mean ± SD

Table 4.

Comparative MRI metrics of patients with or without thalamic lesions

	With thalamic lesions	Without thalamic lesions	p-value*
N	38	52	
Gender (M/F)	11/27	11/41	0.396
Age, years	44.4 (9.4)	41.2 (8.7)	0.107
Disease duration, years	10 (8.9)	8.8 (9.4)	0.312
EDSS score, median (range)	3.5 (8)	2 (7)	**0.021**
SDMT, Z-score	−0.4 (1.6)	0.2 (1.4)	0.064
RRMS:SPMS	20:18	41:11	**0.009**
Leukocortical lesion volume	1512 ± 2214	318 ± 605	0.054
Intracortical lesion volume	6.9 ± 15.3	300 ± 542	**0.002**
Subpial lesion volume	711 ± 864	296 ± 542	**0.002**
White matter lesion volume	6228 ± 10325	3848 ± 5487	0.191
Thalamus volume	4349 ± 792	4583 ± 931	0.198

All values are reported as mean (SD);

*for comparisons between subjects with and without thalamic lesions

Table 5.

Multivariate regression estimates for thalamic atrophy

	Estimate	p-value	95% CI
Intercept	$3.2 \cdot 10^{-3}$	0.18	$-1.5 \cdot 10^{-3}$, $7.8 \cdot 10^{-3}$
Age	$-3.0 \cdot 10^{-6}$	0.59	$-1.4 \cdot 10^{-5}$, $8.1 \cdot 10^{-6}$
Gender	$5.0 \cdot 10^{-4}$	0.65	$-1.7 \cdot 10^{-4}$, $2.7 \cdot 10^{-4}$
Thalamic Lesion Volume	$-6.5 \cdot 10^{-5}$	0.24	$-1.7 \cdot 10^{-4}$, $4.4 \cdot 10^{-5}$
Cortical Lesion Volume	$-3.6 \cdot 10^{-5}$	0.63	$-1.8 \cdot 10^{-4}$, $1.1 \cdot 10^{-4}$
White Matter Lesion Volume	$-2.8 \cdot 10^{-4}$	**0.003**	$-4.6 \cdot 10^{-4}$, $-1 \cdot 10^{-4}$
Cortical Thickness	$1.2 \cdot 10^{-3}$	0.77	$-6.8 \cdot 10^{-3}$, $9.2 \cdot 10^{-3}$