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ORIGINAL
RESEARCH

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BACKGROUND AND PURPOSE: Several studies suggest that grey matter involvement may play a role in multiple sclerosis (MS) pathology. Diffusion tensor imaging (DTI) at 3T was used to investigate the presence of damage to the normal-appearing thalamus in MS and its relationship with disability.

MATERIALS AND METHODS: Twenty-four patients with relapsing-remitting (RR, $n = 13$, age = 41.7 ± 6.1 , Expanded Disability Status Scale [EDSS] score = 2.2 ± 1.2) and secondary-progressive ($n = 11$, age = 46.9 ± 9.6 , EDSS = 5.9 ± 1.0) MS and 24 age- and sex-matched healthy volunteers were studied. Fractional anisotropy (FA) and mean diffusivity (MD) were measured in regions of interest of normal-appearing thalamus. We examined group differences in MD and FA and correlations between DTI-derived metrics and clinical or imaging measures of disease.

RESULTS: Patients with MS had higher thalamic FA ($P < .0001$) and MD ($P = .035$) than volunteers. MD values correlated with the Paced Auditory Serial Addition Task ($r = -0.43$, $P = .034$) and motor EDSS ($r = 0.47$, $P = .021$) scores. In patients with RRMS, MD values correlated with global EDSS ($r = 0.75$, $P = .003$) and motor EDSS ($r = 0.68$, $P = .010$). Correlations were found between MD values and T1 and T2 lesion load ($r = 0.58$, $P < .05$) and brain parenchymal fraction ($r = -0.46$, $P < .05$).

CONCLUSIONS: DTI was able to detect abnormalities in normal-appearing thalamus of patients with MS. The strength of association between thalamic DTI measures and functional impairment was in the same range as those seen with standard MR imaging disease measures. The assessment of the integrity of the thalamus with DTI is a promising metric as a marker of disease for future studies.

MR imaging has revolutionized the diagnosis and follow-up of patients with multiple sclerosis (MS) by providing reliable detection and quantitative estimation of focal white matter (WM) lesions in vivo. WM lesion load, however, is only weakly correlated with the disability of patients with MS.^{1,2} Given the limited sensitivity of conventional MR imaging, researchers oriented their focus also to subtle damage to the so-called normal-appearing WM (NAWM) and normal-appearing gray matter (NAGM), aiming to better explain neurologic impairments of these patients.^{3,4}

Postmortem and in vivo studies have demonstrated that the deep gray matter (GM) is also affected in MS. Diffuse microscopic damage in the absence of macroscopic MS lesions can be present in the thalamus and basal ganglia.^{5,6} The thalamus, in particular, is a critical structure for a wide range of neurologic functions, including motor, sensory, and cognitive abilities.⁷ Because thalamic axons convey information between multiple, subcortical, and specific cortical regions, both direct microstructural damage to thalamic nuclei and indirect

changes induced by axonal degeneration secondary to WM MS lesions could be intimately related to functional disability in MS.

Previous studies have used high-resolution volumetric MR imaging metrics, MR spectroscopy, and diffusion-weighted and magnetization-transfer imaging to investigate the thalamus of patients with MS, but a number of issues still remain unresolved. Some studies found no differences between patients with MS and healthy controls,⁸⁻¹⁰ whereas others suggested that thalamic involvement is detectable in patients with MS.^{5,11-17} The time course of thalamic involvement in MS is still an unanswered question. Although some studies have suggested that thalamic involvement starts early,^{14,18,19} others have only identified damage in later stages of the disease.¹⁵

Diffusion tensor imaging (DTI) describes the properties of water diffusion in vivo, thus disclosing important details of fiber tract orientation and providing information regarding microstructural integrity of the tissue.²⁰⁻²³ Few studies have used DTI^{9,10,24} to investigate thalamic changes in MS. However, results have been conflicting, and the relationship between DTI-derived metrics pointing to thalamic involvement and functional disability remains unclear. The use of improved methods, including high-field MR imaging, may be relevant in this setting. A recent volumetric/DTI study showed advantages of 3T MR imaging in detecting atrophy and diffusivity abnormalities in the NAWM and NAGM of patients with MS.²⁵ In fact, it has been shown that the increased signal intensity-to-noise ratio (SNR) provided by high-field MR imaging and multiaarray coils can have a direct impact on the quantitative measurements obtained by DTI.^{26,27}

On the basis of the notions that 1) MS pathology is typically diffuse and 2) that the thalamus is a convergence zone densely interconnected with most cortical regions, we hypothesized

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Table 1: Demographic, clinical, and MR imaging characteristics of healthy volunteers and patients*

	HV (<i>n</i> = 24)	RR (<i>n</i> = 13)	SP (<i>n</i> = 11)
Age (yr)	41.9 ± 8.3	41.7 ± 6.1	46.9 ± 9.6
EDSS	—	2.2 ± 1.2†	5.9 ± 1.0†
EDSS-motor	—	1.7 ± 1.1†	3.5 ± 0.8†
EDSS-sens	—	1.2 ± 1.0‡	2.2 ± 0.9‡
DD	—	11.1 ± 6.5‡	17.6 ± 4.7‡
PASAT	—	47.5 ± 15.9	37.1 ± 11.1
T1LV	—	3.82 ± 3.43	6.08 ± 3.70
T2LV	—	14.41 ± 10.79	17.89 ± 14.95
BPF	0.84 ± 0.02§	0.80 ± 0.04‡§	0.75 ± 0.04‡§
CELS	—	1	0
Thalamic FA	0.276 ± 0.017	0.307 ± 0.022§	0.308 ± 0.017§
Thalamic MD	0.737 ± 0.019	0.751 ± 0.046	0.764 ± 0.028

Note: — indicates not applicable; HV, healthy volunteers; DD, disease duration; CELs, number of patients with contrast-enhancing lesions; EDSS-sens, partial sensory score of the EDSS; EDSS, Expanded Disability Status Scale; PASAT, Paced Auditory Serial Addition Task; BPF, brain parenchymal fraction; LV, lesion volume; FA, fractional anisotropy; MD, mean diffusivity; RR, relapsing-remitting; SPMS, secondary-progressive multiple sclerosis. * Data are mean ± SD. T1LV and T2LV are given in cubic centimeters, BPF and FA values are dimensionless, and MD values are given in mm²/s × 10^{−3}.

† *P* < .001, comparison between RR and SPMS.

‡ *P* < .05, comparison between RR and SPMS.

§ *P* < .001, compared with HVs.

|| *P* < .05, compared with HVs.

that subtle thalamic damage (not visible in standard MR imaging techniques), when present, could significantly explain the functional disability of patients with MS. We also reasoned that using high-resolution 3T DTI data acquisition and improved image processing would yield improved tissue characterization. In the present study, we investigated the existence of subtle damage in the normal-appearing thalamus of patients with MS and quantified the impact of these potential changes in motor and cognitive clinical disability.

Materials and Methods

Subjects and Study Design

This is a cross-sectional study performed at the Neuroimmunology Branch of the National Institute of Neurologic Disorders and Stroke and approved by the institutional review board. All participants gave informed written consent.

Twenty-four patients with MS according to the Poser et al criteria²⁸ and classified as having relapsing-remitting MS (RRMS) (*n* = 13) or secondary progressive MS (SPMS) (*n* = 11)²⁹ were consecutively enrolled in the study. The exclusion criteria for the study were the following: 1) inability to provide a written consent form, 2) contraindication to undergo a 3T MR imaging, and 3) the presence of clinical relapse or steroid treatment within 1 month of the study.

Patients had a neurologic examination performed by an examiner blinded to their MR imaging characteristics. The Expanded Disability Status Scale (EDSS)³⁰ and the 3-second version of the Paced Auditory Serial Addition Task (PASAT)^{31,32} scores were used to assess the physical and cognitive ability of patients. Twenty-four healthy volunteers, age- and sex-matched to the patient group, were recruited and scanned by using the same protocol. To evaluate interscan variability, 4 volunteers were rescanned using the same DTI protocol 2 weeks apart, and an interscan coefficient of variation (COV) was obtained.

Clinical, demographic, and MR imaging characteristics of volunteers and patients with RR- and SPMS are summarized in Table 1. Although patients were consecutively enrolled, our cohort of patients with RRMS had relatively mild disability. At the time of the study, 6

patients were on chronic immunomodulatory therapy, whereas 9 patients were on immunosuppressive therapy.

MR Imaging Acquisition

MR imaging was performed on a 3T scanner (Signa Excite HDx; GE Healthcare, Milwaukee, Wis) by using an 8-channel high resolution head coil (Invivo Corp, Gainesville, Fla). The following sequences were acquired in the axial plane: 1) spin-echo (SE) T1-weighted (T1WI) with 54 contiguous sections of 2.4-mm thickness, TR/TE = 700/11 ms, matrix = 256 × 256, FOV = 240 × 240 mm, before and within 10 minutes of injection of a single dose of gadopentate dimeglumine (Magnevist; Berlex Labs, Cedar Knolls, NJ); 2) fast SE (FSE) T2-weighted (T2WI) with 54 contiguous sections of 2.4-mm thickness, TR/TE = 5100/120 ms, matrix = 256 × 256, and FOV = 240 × 240 mm; 3) T1WI 3D inversion-recovery fast-spoiled gradient echo (IR-FSPGR) with TR/TE = 7.5/3 ms, matrix = 256 × 256, FOV = 240 × 240 mm, TI = 750 ms, flip angle = 16°, bandwidth = 31.25 kHz with 1.0-mm thickness; and 4) 2 DTI acquisitions by using a single-shot SE echo-planar imaging (EPI) sequence with 54 contiguous sections of 2.4-mm thickness, TR/TE = 13,000/76 ms, matrix = 96 × 96 (reconstructed to 256 × 256), FOV = 240 × 240 mm, with array spatial sensitivity encoding technique acceleration factor of 2. The DTI acquisition consisted of 3 volumes with no diffusion gradients applied (*b*=0) and 33 volumes with diffusion gradients applied in noncollinear directions, with *b*=1000 s/mm². The volunteers underwent the same MR imaging protocol with the exclusion of the postcontrast T1WI sequence.

Postprocessing

T1 and T2 Lesion-Volume Computation. T2 hyperintense and T1 hypointense lesion number and volume were marked by 2 independent observers by using a semiautomated local threshold method in MEDx (Medical Numerics, Gaithersburg, Md).³³ A chronic T1-hypointense lesion was defined as any hypointense region visible on the T1WI image with a corresponding hyperintense region on the T2WI image in the absence of corresponding contrast enhancement.³⁴ Contrast-enhancing lesions were counted from hard copies.

Brain Parenchymal Fraction Computation. The 3D-IR-FSPGR images were used to calculate automatically brain parenchymal fraction (BPF), by using the structural image evaluation, with normalization of atrophy (SIENAX) software (<http://www.fmrib.ox.ac.uk/fsl/siena/index.html>).³⁵

DTI Analysis. After correction for movement and EPI-induced distortion artifacts,^{36,37} image data were inspected for any apparent artifacts. The diffusion tensor was calculated for each voxel and decomposed into eigenvalues and eigenvectors by using multivariate fitting. MD and FA maps were then produced in DTIStudio software, Version 6.9 (<https://www.mristudio.org>).³⁸

Region-of-Interest Placement. For each subject, the T2WI and T1WI images were registered to the first (*b*=0) image by using a 12-parameter affine registration algorithm.³⁷ The thalamus was inspected for the presence of lesions on both the registered and unregistered T1WI and T2WI images. In each hemisphere, 2 symmetric circular regions of interest (area = 68 pixels, including mainly the centromedian, dorsoventral, and dorsolateral regions of the thalamus)^{22,24} were placed in the normal-appearing thalamus on 3 consecutive axial sections (above the plane of the anterior commissure) on the (*b*=0) image and examined in all 3 planes by 1 investigator. Care was taken to ensure that the thalamus could be identified bilaterally on at least 1 section dorsally and 1 section caudally from the target

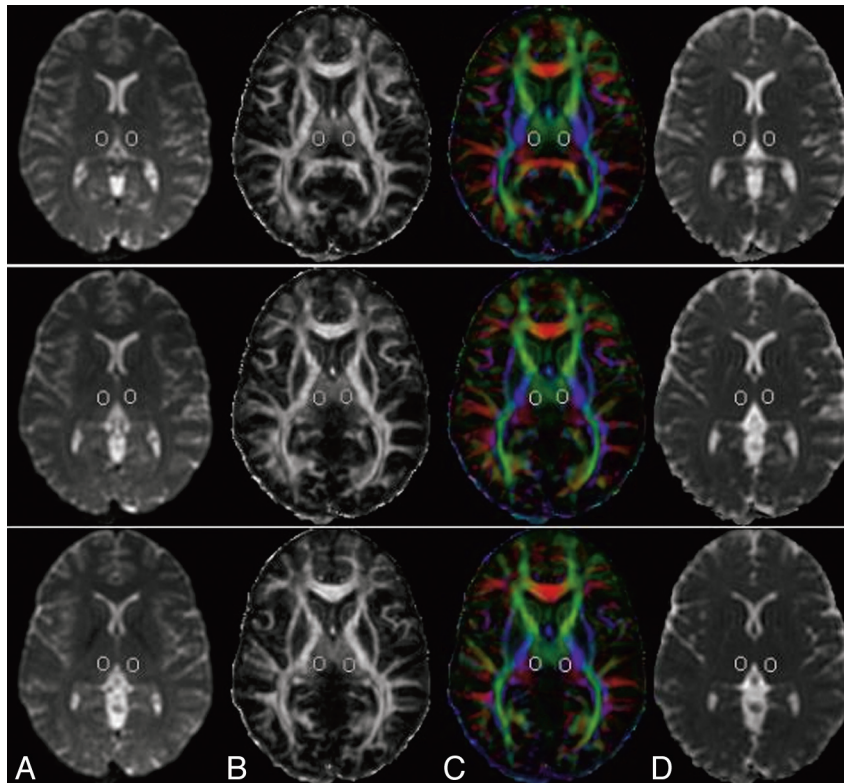


Fig 1. Bilateral thalamic regions of interest placed in 3 consecutive levels (sections) in the axial plane of a representative healthy volunteer. *A*, $b=0$ image. *B*, FA. *C*, Color-coded FA. *D*, MD maps.

sections so that no adjacent structures were included (Fig 1). The regions of interest were overlaid on the FA and MD maps, and mean thalamic FA and MD values were obtained from the average across the 3 regions of interest between the right and left hemisphere values.

To evaluate potential intraobserver variability, we repeated all postprocessing steps in 5 patients and 5 volunteers, chosen randomly, 2 weeks from the first measurements, and intraobserver COV was obtained. Interobserver COV was also obtained by a second investigator by placing regions of interest within the thalamus on FA and MD maps in 5 patients and 5 volunteers, by using the same methodology.

Statistical Analysis

A 2-sample t test was used to test differences in mean thalamic FA values between patients with MS and volunteers. A Welch variance-weighted 2-sample t test, accounting for the heterogeneous variances of thalamic MD values, was performed to investigate differences between patients with MS and volunteers.

Regression analysis was used to investigate the effect of age on FA and MD values of each of the 3 groups (volunteers, RR, and SP) before comparing the 3 groups. Analysis of variance (ANOVA) and Welch variance-weighted ANOVA were used as appropriate to test differences in mean thalamic FA and MD values among the 3 groups, followed by a post hoc multiple pair-wise comparisons with Bonferroni correction. P values $< .0167$ were considered significant for multiple comparisons after Bonferroni correction. Correlation analyses were conducted by using the Pearson correlation coefficient to investigate relations between DTI-derived metrics and clinical or other MR imaging metrics. Significance was established at an α level of 0.05. COV, given as an SD divided by the mean as a percentage, was used to evaluate the interscan, intra-, and interobserver variability. Statistical

analysis was performed by using the SAS software Version 9.1 (SAS Institute, Cary, NC).

Results

No abnormalities were found in the conventional MR imaging examinations of volunteers. No T1WI, T2WI, or contrast-enhanced lesions were found in the thalamus in any of the patients and volunteers. The interscan ($COV_{FA} = 4.0\%$; $COV_{MD} = 2.1\%$), intraobserver ($COV_{FA} = 1.3\%$; $COV_{MD} = 0.2\%$), and interobserver ($COV_{FA} = 0.8\%$; $COV_{MD} = 0.4\%$) variability results showed good reproducibility.

Differences in FA and MD Values between Patients with MS and Volunteers

As shown in Table 1, thalamic FA ($P < .0001$) and MD ($P = .035$) values were higher in patients than in volunteers.

When patients with RR- and SPMS were examined as separate cohorts, age effect was not significant on either FA ($P = .81$) or MD ($P = .66$) values. Thus we examined differences in mean FA and MD values among the 3 groups without considering the effect of age.

Among the 3 groups, significant differences were found in mean FA ($P < .0001$) and MD ($P = .0324$) values. Specifically for FA values, there was a significant difference between volunteers and patients with RRMS ($P < .0001$), between volunteers and patients with SPMS ($P < .0001$), but not between patients with RRMS and SPMS ($P = .94$). A significant difference was found in MD values between volunteers and patients with SPMS ($P = .002$), but not between either volunteers or patients with RRMS ($P = .34$) or patients with RRMS and SPMS ($P = .40$).

Table 2: Pearson correlation coefficient between DTI-derived metrics (FA and MD) and clinical and MR imaging metrics

	All MS (<i>n</i> = 24)		Patients with RRMS (<i>n</i> = 13)		Patients with SP (<i>n</i> = 11)	
	FA	MD	FA	MD	FA	MD
DD	0.291	0.132	0.187	0.06	0.638*	0.018
EDSS	0.174	0.351	0.193	0.748*	0.545	−0.475
EDSS-motor	0.287	0.468*	0.396	0.683*	0.340	−0.049
EDSS-sens	0.087	0.317	−0.019	0.535	0.286	−0.328
PASAT	−0.042	−0.434*	−0.235	−0.502	0.400	−0.122
T1LV	0.321	0.584*	0.318	0.534	0.325	0.804*
T2LV	0.481*	0.582*	0.544	0.562*	0.439	0.784*
BPF	−0.093	−0.458*	−0.293	−0.521	0.208	−0.292

Note:—All MS indicates all patients with multiple sclerosis.

*Correlations at a significance level of .05. FA values are dimensionless; MD values are given in $\text{mm}^2/\text{s} \times 10^{-3}$.

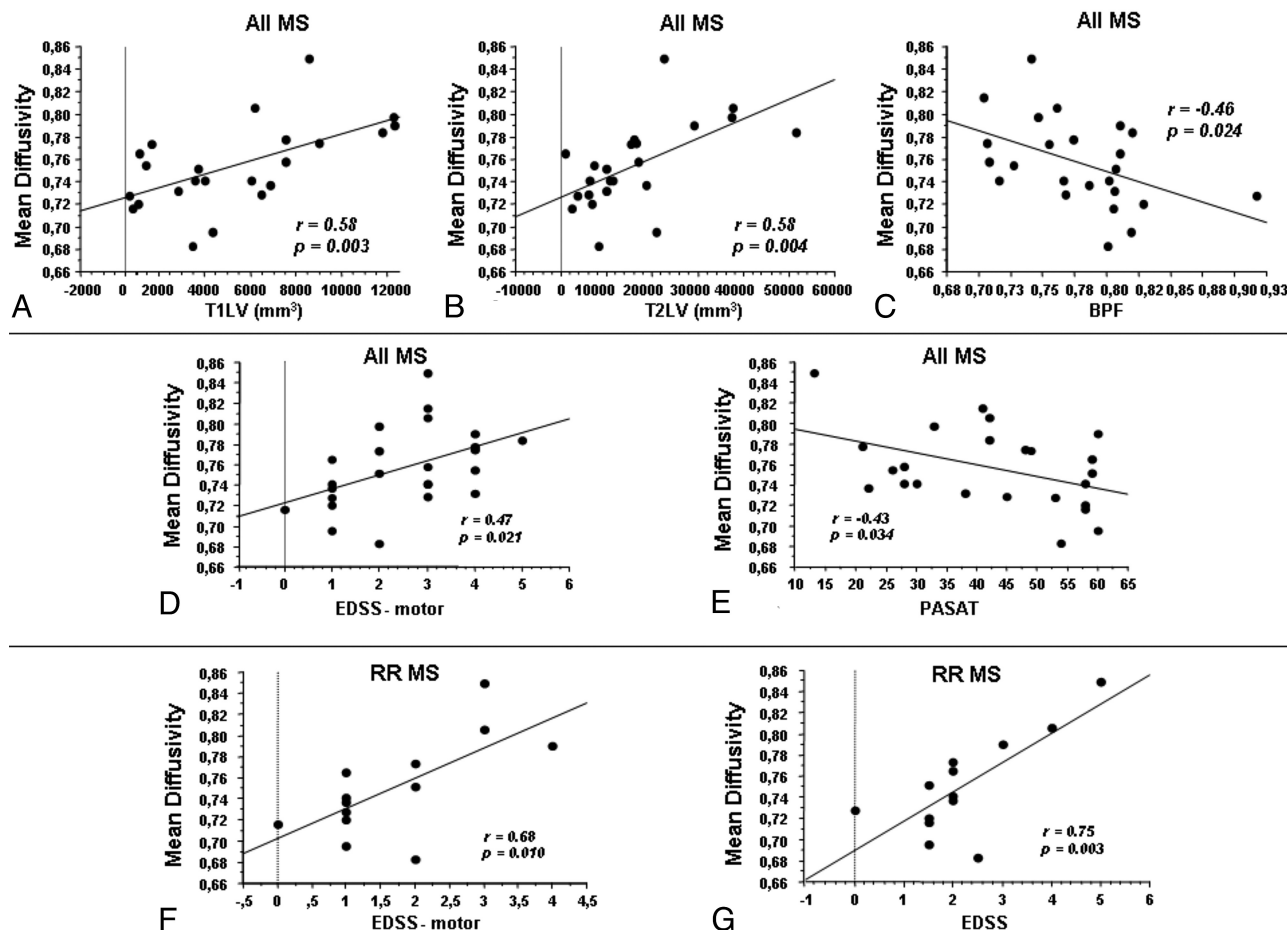


Fig 2. Correlation plots between MD values and T1LV (A), T2LV (B), BPF (C), EDSS-motor (D), and PASAT (E) in the entire cohort of patients with MS (All MS). Correlation plots between MD values and EDSS-motor (F) and EDSS (G) in patients with RRMS. Note that MD values are given in $\text{mm}^2/\text{s} \times 10^{-3}$.

Correlation between FA and MD and Other MR Imaging Metrics

Details on the correlation analysis between thalamic FA and MD values and T1 and T2 lesion volumes (LV) and BPF are described in Table 2. A significant correlation was found between thalamic FA and T2LV in the entire group of patients ($r = 0.48$, $P = .020$). However, a correlation was not found when patients with RR- and SPMS were considered separately.

Thalamic MD was correlated with T1LV ($r = 0.58$, $P = .003$), T2LV ($r = 0.58$, $P = .004$), and BPF ($r = -0.46$, $P = .024$) in the entire group of patients (Fig 2A–C). When con-

sidering patients with RR- and SPMS separately, MD values were significantly correlated with T2LV in patients with both RR ($r = 0.56$, $P = .046$) and SP ($r = 0.78$, $P = .007$) and with T1LV only in the SP group ($r = 0.80$, $P = .005$).

Correlation between Thalamic FA and MD Values and Clinical Scores

Disease duration did not significantly affect DTI-derived metrics in the entire group of patients. In the same cohort, significant correlations were observed between the motor EDSS ($r = 0.47$, $P = .021$) and PASAT ($r = -0.43$, $P = .034$) scores and MD (Fig 2D–E). No correlations were found with the FA values.

When patients with RR- and SPMS were considered separately, correlations were found between thalamic MD and functional scores of patients with RR only. Disease duration was significantly related to thalamic FA changes only in the patients with SP, whereas in the patients with RR, MD values were strongly correlated with motor-specific EDSS score ($r = 0.68$, $P = .010$) and EDSS ($r = 0.75$, $P = .003$) (Fig 2F–G).

Discussion

The role of GM disease, alone or together with WM damage, in explaining patients' disabilities and in predicting disease progression in MS is becoming more evident.^{39–41} Primary or secondary damage of thalamic tissue and/or radiations may have an important impact in a patient's disability, due to the existence of massive reciprocal connections between thalamic nuclei and several cortical areas.^{7,42}

We used 3T DTI to investigate structural thalamic changes in patients with MS. We directed our focus to the thalamus because of its unique mixed WM and GM composition and its massive interconnection with several cortical and WM systems of the brain. The main findings were the following: 1) DTI-derived metrics were sensitive to detect thalamic damage, 2) increase in thalamic MD correlated with cognitive and motor scores when all patients with MS were considered, and 3) in patients with RRMS, thalamic involvement explained patient disability to a large degree. These findings are discussed below.

Sensitivity of DTI in Detecting Thalamic Involvement in Patients with MS

Patients with MS exhibited higher FA values compared with volunteers, when considering the whole MS group or SPMS and RRMS separately. These results confirmed previous findings of increased FA values in the thalamus and basal ganglia of patients with MS.²⁴ In our study, FA values also differed between the subgroup of patients with RR-MS and volunteers, indicating that subtle thalamic damage can be present in patients with mild disease. Supporting this finding, thalamic atrophy was demonstrated in patients with early disease,^{14,18} and decreased thalamic metabolism was observed in patients with RR with low disability scores compared with matched volunteers.¹⁹

The increased thalamic FA effect is by itself a topic for further scientific inquiry. The results of the present study are, nevertheless, in agreement with preliminary evidence reported in previous studies.²⁴ Most interesting, a recent study found increased interthalamic connectivity in patients with early MS as measured by DTI and tractography when compared with control subjects, suggesting a possible reactive structural reorganization of the fiber tracts within the thalamus.⁴³ Together with these previous lines of evidence, our findings, though still preliminary, support the possibility that neuroplasticity/responsive reorganization of thalamic circuits might occur in patients with MS. Certainly, the biologic basis of this effect remains poorly understood. Interpreting small anisotropy changes in the thalamus in which several fiber pathways typically intersect is a difficult task,^{21,24,44} which will require validation by combined MR imaging and postmortem studies.

Contrary to previous studies,^{9,10,24} our study showed increased thalamic MD both in the whole group of patients and

in the SP subgroup. Griffin et al⁹ reported no MD changes in patients with early MS (RR) (median EDSS score of 1.0) compared with controls, in agreement with our findings. Ciccarelli et al²⁴ found no differences between thalamic MD of patients with MS and controls. However, their cohort also included patients with primary-progressive (20%) and benign MS (28%), which often exhibit less brain damage. In contrast, Filippi et al¹⁰ did not report an increase in thalamic MD of patients with MS with disability scores and MS subtypes comparable to ours. Possibly, the higher resolution DTI technique and improved preprocessing steps, such as correction for movement artifacts and EPI-induced distortions,^{26,27} used in our study may have accounted for these differences.

Other MR imaging methods have also demonstrated thalamic abnormalities in MS. A decreased magnetization transfer rate was reported in patients with MS,¹⁵ as well as decreases in *N*-acetylaspartate, a neuronal marker.^{16,45} These findings point to loss of tissue integrity and concur with the demonstration of axonal tract damage in histopathologic studies.^{5,46} Increased MD values in the thalamus most likely correspond to an increased water component, which agrees with the possibility of demyelination and/or axonal damage.

Correlation between DTI-Derived and Other MR Imaging Metrics

Correlations were found between DTI-derived metrics in the thalamus and remote WM damage reflected by T2LV (MD and FA), T1LV (MD), or BPF (MD). In accordance, increase in thalamic myo-inositol was also shown to be correlated to WM T2 lesion load in a spectroscopy study of patients with MS.¹⁶ Because several WM tracts connect the thalamus with different cortical regions, 1 plausible hypothesis would be that structural damage to WM networks could induce trans-synaptic axonal degeneration within thalamic nuclei. Yet, whether the relation of the 2 processes is causal or indirect remains uncertain.

Relationship between DTI-Derived Metrics and Clinical Scores

The thalamus is densely interconnected with practically all the cortical regions.^{7,42,47} Thus, thalamic damage can potentially trigger a range of motor and cognitive dysfunctions in patients with MS. Our results support this hypothesis because motor EDSS and PASAT were significantly correlated to MD changes in the thalamus of the whole group of patients in our study. In the RR subgroup, MD was strongly correlated to EDSS and motor EDSS, and a trend was observed with sensory EDSS and PASAT. Remarkably, the increase in thalamic MD explained the 55% of variance in EDSS in patients with RRMS. Future studies by using thalamic nuclei segmentation and correlation to regional WM disease will be crucial for understanding whether changes in thalamic MD are topographically related to damage or dysfunction of specific thalamocortical networks.

Although our DTI measures were obtained from a restricted volume of the brain (the thalami), correlations with MS disability scores were at least as strong as those reported in previous studies using whole-brain lesion counting (T1 or T2LV).^{1,2} Additional studies using larger samples might explore to what degree thalamic DTI measures, whole-brain T1

or T2LV, and whole-brain atrophy overlap in explaining MS disability. This could be addressed by doing stepwise regression analyses while entering these different measures as independent predictors.

No significant correlations between clinical scores and DTI-derived metrics were observed in the SPMS group. Two possible explanations for this negative finding are the following: 1) the functional disability scores being high but restricted within a narrow range (between 5.0 and 7.5), therefore reducing the variance due to a ceiling effect; and 2) the reduced power given the relatively small number of patients included in this subgroup. Furthermore, the disability of patients with SPMS may be driven by spinal cord pathology. A larger cohort of patients with wider ranges of functional scores may confirm and extend our results.

Disease duration was not correlated to changes in FA or MD in patients with MS, except for a moderate correlation between disease duration and FA changes in the SPMS group. This result supports the view that structural damage is more related to the severity of functional impairment than to the duration of the disease.

Conclusions

The 3T DTI can reveal microstructural damage in the normal-appearing thalamus of patients with MS. MD was correlated with motor and cognitive symptoms in patients with MS and strongly correlated with disability in the RR group. MD was also moderately correlated with WM lesion load. It is, therefore, possible that both direct and indirect damage to the thalamus occurs in MS. Future studies addressing the relationship between noninvasive imaging and histopathology will be necessary to explain the exact pathological correlates of thalamic involvement in patients with MS.

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