Clinically Isolated Syndrome Suggestive of Multiple Sclerosis:
Voxelwise Regional Investigation of White and Gray Matter

Eytan Raz, MD
Mara Cercignani, PhD
Porzia Totaro, MD
Carlo Pozzilli, MD
Marco Bozzali, MD
Patrizia Pantano, MD

Purpose:
To quantify white matter (WM) and gray matter (GM) damage in patients who presented with clinically isolated syndrome (CIS), which is suggestive of multiple sclerosis (MS), by combining volume-based morphometry (VBM) and tract-based spatial statistics (TBSS).

Materials and Methods:
This prospective HIPAA-compliant study was approved by the institutional review board. Written informed consent was obtained from all participants. In this study, 34 consecutive patients (21 women, 13 men; mean age, 31.7 years ± 7.7 [standard deviation]) who presented with CIS were recruited. The magnetic resonance (MR) examination included dual-echo fast spin-echo, three-dimensional T1, and diffusion-tensor imaging. Sixteen matched healthy volunteers served as control subjects. T2 lesion volumes were assessed with a semiautomatic technique. VBM and TBSS were used for the GM and WM analyses, respectively, to compare regional GM volumes and fractional anisotropy (FA) values in the two groups.

Results:
TBSS analysis revealed a pattern of diffuse FA reductions in patients with CIS at the cluster level (P < .05). Regions of decreased FA involved most of the WM pathways, including the corticospinal tracts, corpus callosum, and superior and inferior longitudinal fasciculi. There were no significant differences between the two groups in terms of global GM, WM, or cerebrospinal fluid volume or in terms of regional GM volume.

Conclusion:
Diffuse WM damage not accompanied by any change in GM or WM volume is observed in patients with CIS. This suggests that WM involvement plays a relevant role in the early phases of MS. Subsequently detected GM damage may be secondary to WM alterations.

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It is well known that T2 lesion volumes on magnetic resonance (MR) images correlate poorly with the clinical status of patients with multiple sclerosis (MS). This lack of correlation is mainly due to the presence of additional microscopic abnormalities in the so-called normal-appearing white matter (NAWM) and normal-appearing gray matter (NAGM) (1,2). Two mechanisms have been proposed as the principal causes of damage in the normal-appearing brain tissue of patients with MS: The first is the presence of microscopic demyelinating lesions in both white matter (WM) and gray matter (GM). The second is neurodegeneration of axons and neurons. Whether these mechanisms play different roles in different stages of the MS course remains a matter of debate. An insight into the early expression of MS can be obtained by applying quantitative MR techniques in patients who present with a clinically isolated syndrome (CIS). CIS is defined as the first acute neurologic event suggestive of MS (optic neuritis, brainstem syndrome, spinal cord syndrome) in the absence of any alternative diagnosis (3).

Diffusion-tensor imaging (DTI) is one of the MR techniques most often used to assess the integrity of WM tracts and, in particular, the quantification of fractional anisotropy (FA), which is an index of tissue organization at the subvoxel level (4). DTI has been used extensively to study patients with CIS, although previous studies have been based on the analysis of a priori selected regions of interest or histograms (5–7). A diffuse disease, however, ideally requires a method of analysis that combines the spatial specificity of region-of-interest analysis with the possibility of assessing the whole brain, such as a voxel-based analysis. A tool for voxel-based analysis of DTI data, called tract-based spatial statistics (TBSS), was developed relatively recently (8). In patients with clinically definite MS, TBSS revealed widespread areas of reduced FA in WM (9,10), as well as an association between regional FA and cognitive performance (11).

Similarly, the spatial distribution of GM atrophy can be assessed by means of voxel-based morphometry (VBM), which is an operator-independent and unbiased tool used in MR image analysis that reflects the regional GM volume at a voxel scale (12).

The aim of this work was to quantify WM and GM damage in patients who presented with CIS, which is suggestive of MS, by combining VBM and TBSS.

Materials and Methods

Patients

Our study was approved by the institutional review board of Sapienza University of Rome and complied with the health insurance portability and accountability act. Written informed consent was obtained from all participants.

For this prospective study, we selected 39 consecutive patients who were referred to the MS center at our institution between April 2006 and March 2008 and met the following inclusion criteria: They had a single clinical episode indicative of MS (optic neuritis, brainstem syndrome, spinal cord syndrome), and they were between 18 and 50 years of age. The exclusion criteria were as follows: any alternative diagnoses to MS, the presence of other relevant diseases, and contraindications to MR imaging.

Five patients were excluded on the basis of the exclusion criteria: One received a diagnosis other than MS; one had other relevant diseases, and three had contraindications to MR imaging. The remaining 34 patients were included in the study.

All patients underwent a detailed neurologic examination (C.P., E.S.; a board-certified neurologist with 25 years of experience and a 4th-year resident in neurology, respectively).

The following demographic and clinical variables were collected for each patient: age, level of disability as assessed with the Kurtzke Expanded Disability Status Scale (EDSS) (13), and symptom onset. The 34 patients had a mean age of 31.7 years ± 7.7 (standard deviation) and a median EDSS score of 1.5 (range, 0–3). Of these patients, 21 were women (mean age, 31.7 years ± 7.8), and 13 were men (mean age, 32.0 years ± 7.9). Two patients presented with cerebral symptoms; three, with brainstem symptoms; three, with cerebellar symptoms; six, with retrobulbar symptoms.

Advances in Knowledge

- Use of a voxelwise approach reveals white matter (WM) damage without significant gray matter (GM) loss in patients with clinically isolated syndrome, which is suggestive of multiple sclerosis (MS).
- The WM tracts affected by the disease processes in the earliest stage of MS are the corpus callosum, corticospinal tracts, and long association fibers.

Implication for Patient Care

- We propose an unbiased method of image analysis for global assessment of WM and GM tissue damage in patients who present with a first clinical episode suggestive of MS that may yield useful clinical information.
optic neuritis; and 18, with spinal cord symptoms. Two patients had a multisymptomatic onset.

Within three months of the acute event, all patients underwent an MR examination that included conventional imaging, three-dimensional T1 imaging, and DTI, as will be discussed later in this article.

Sixteen healthy volunteers (mean age, 38.0 years ± 12.2), 12 of whom were women (mean age, 38.0 years ± 13.6) and four of whom were men (mean age, 37.7 years ± 6.0), with no known brain abnormalities and no neurologic symptoms were recruited as control subjects.

MR Image Acquisition

All participants underwent imaging with a 1.5-T MR imager (Gyroscan NT 15; Philips Medical Systems, Best, the Netherlands). The body coil was used for signal transmission, and the manufacturer-provided 16-channel head coil designed for sensitivity encoding was used for signal reception. Section orientation parallel to the subcallosal line was assured by acquiring a multiplanar T1-weighted localizer at the beginning of each study (14). The following sequences were performed during a single session for all subjects: (a) an axial dual-echo fast spin-echo sequence on 48 contiguous 3-mm-thick sections (repetition time msec/echo time msec, 2150/30 and 120; echo train length, 12; matrix, 256 × 256; field of view, 250 mm²; sensitivity encoding reduction factor, 1.4; acquisition time, 5 minutes 48 seconds); (b) a three-dimensional T1-weighted fast field-echo sequence on 150 contiguous axial 1-mm-thick sections (40/4; flip angle, 30°; matrix, 512 × 512; field of view, 240 mm²; sensitivity encoding reduction factor, 1; acquisition time, 7 minutes 18 seconds); and (c) DTI with a single-shot echo-planar pulse sequence on 25 contiguous 5-mm-thick sections (3694/95; 128 × 128 matrix, field of view, 250 mm²; sensitivity encoding reduction factor, 2.5; acquisition time, 8 minutes 31 seconds). Diffusion-sensitized gradients were applied along six noncollinear directions by using two b values (0 and 1000 sec/mm²), and amplitude images were averaged from 10 measurements.

Image Analysis and Postprocessing

Image data processing was performed by an MR imaging physicist (M.C., 10 years of experience) and a resident in radiology (E.R., 4 years of experience), neither of whom was aware of the clinical data, on a personal computer running Jim 4.0 software (Xinapse System, Leicester, England), the FMRIB Software Library 4.0 software package (FMRIB Image Analysis Group, Oxford, England) (15), MATLAB 7.0 software (Mathworks, Natick, Mass), and Statistical Parametric Mapping 5 software (Wellcome Department of Cognitive Neurology, London, England).

Lesion volume.—Lesion volumes were obtained by using a semiautomatic technique based on local thresholding (16). Lesions were segmented on proton-density images, while T2-weighted images were always used to increase the confidence level of lesion identification. The lesion volume yielded the following data for every subject: a quantification of the lesion burden and a binary lesion mask needed to perform TBSS and VBM analyses (17). Lesion masks were then transformed into standard space and averaged to yield a mean lesion mask across subjects.

TBSS and mean FA.—Maps of FA were computed for all subjects from the diffusion-tensor images after eddy current correction and automatic brain extraction by using the FMRIB Diffusion Toolbox, which is part of the FMRIB Software Library (8). FA maps were fed into the TBSS tool, which is also part of the FMRIB Software Library. TBSS analysis consisted of four steps: The FA data of all subjects were aligned into a common space by means of nonlinear registration (18), and the mean FA image was created and thinned to obtain a mean FA skeleton, which represented the centers of all tracts common to the group. Each subject’s aligned FA data were then projected onto this skeleton, and the resulting data were fed into a voxelwise cross-subject statistical analysis, which was performed to enable us to identify differences in the FA areas between patients and healthy control subjects. To yield an estimate of the quantitative differences in FA between patients and control subjects, we created a colorimetric map that represented each group’s mean FA values across the designed skeleton. Because the process of skeletonization in TBSS relies on identification of the maximum FA value in a direction perpendicular to the direction of the tract as derived from the average skeleton, it is difficult to predict the effect of MS lesions on the skeletonized FA maps. Therefore, we decided to restrict our analysis to the NAWM by removing from analysis all voxels in which at least 10% of the patient population had a lesion (based on the mean lesion mask). We performed voxelwise analysis by using permutation-based inference (2000 permutations) corrected for multiple comparisons with a cluster threshold (t = 3) and a corrected cluster size significance level of P < .05. For each patient, we computed the mean skeleton FA as summary statistics for further analysis.

Volumetric assessment.—Three-dimensional T1 images underwent automated segmentation to yield GM, WM, and cerebrospinal fluid (CSF) images (19). The VBM protocol consisted of an iterative combination of segmentations and normalizations and produced a GM probability map (20). Normalized GM images were modulated (multiplied by the local value derived from the deformation field [19]), thereby preserving within-voxel volumes that might have been altered during nonlinear normalization. For patients, lesions masks were used to remove lesion tissue erroneously classified as GM from the output of segmentation. GM, WM, and cerebrospinal fluid (CSF) volumes were recorded and used to calculate intracranial volume (ICV) with the following equation: ICV = GM + WM + CSF. The brain parenchymal fraction (BPF) was calculated as follows: (GM + WM)/ICV. Data were smoothed by using a 12-mm full width at half maximum Gaussian kernel. Voxelwise comparison of the GM volume in patients with that in control subjects was performed by using an analysis of
covariance adjusted for ICV. P values less than .05 were considered to indicate a significant difference at the voxel level after correction based on the family-wise error correction for multiple comparisons (21).

**Statistical Analysis**

Statistical analysis was performed by an author (P.T., 6 years of experience) using SPSS software (version 16.0; SPSS, Chicago, Ill.) and applying the unpaired t test for differences between groups. Spearman rank correlation coefficients were used to test the relationship of FA values with the EDSS and lesion volume.

**Results**

There were significant differences between patients and healthy volunteers with respect to age and sex. The mean lesion volume of patients was 3.2 mL ± 3.9.

**Mean FA and TBSS**

When patients were compared with healthy control subjects, the mean skeleton FA in the former (0.41 ± 0.02) was significantly lower ($P < .01$) than that in the latter (0.48 ± 0.04). Widespread reductions in FA can also be seen in Figure 1, which shows the mean FA of control subjects and patients across the skeleton. TBSS showed a widespread pattern of significant reductions in the FA of patients with CIS when compared with that in control subjects. Clusters of FA reductions involving more than 10 voxels were found in 73 WM locations distributed bilaterally throughout the whole brain (Fig 2). The coordinates of the 20 largest clusters of reduced FA are shown in Table 1. They involved, above all, the corticospinal tracts, corpus callosum, superior longitudinal fasciculi, inferior longitudinal fasciculi, and thalami, as shown in Figure 2. Mean FA values did not correlate with EDSS or lesion volume.

**Discussion**

This study combines, to our knowledge for the first time, a whole-brain imaging investigation (lesions, NAWM, and NAGM) in patients who are in the earliest clinical stages of MS, as determined with unbiased methods of image analysis. The main finding of this study is that there is a widespread pattern of abnormalities in the NAWM, as evidenced by the reduction in FA, with no corresponding atrophy in the GM, as evidenced by VBM.

This work provides insight into early expressions of MS. In this decade, there has been considerable effort aimed at shedding more light on NAWM and NAGM abnormalities in patients with MS (2,3). Although histopathologic analysis is, in theory, the most informative approach to understanding these pathophysiologic events, postmortem tissue from patients in the earliest stages of MS is rarely available. An MR evaluation may, however, be used as a surrogate marker of pathologic damage.

The fact that this study was conducted in a consecutive series of 34 patients with symptoms suggestive of a first episode of MS has two advantages: First, patients with early-stage MS are not biased by the treatment and chronic expression of the disease. Second, studying MS in its early stages offers the possibility of identifying predictive markers of the future clinical course.

DTI is considered a useful marker of pathologic damage as seen in postmortem studies of subjects who had MS owing to the opportunity it offers to assess microscopic tissue properties (not accessible with conventional MR imaging) (22,23). The study results enabled us to confirm the high sensitivity of DTI in the detection of WM abnormalities not only in patients with clinically definite MS but also in patients with CIS.

The TBSS analysis revealed diffuse FA changes in the WM of patients with CIS in almost the whole skeletonized FA map, even when a cluster-level correction of $P < .05$ was used. This pattern of abnormalities extensively involves the principal WM bundles (the corticospinal tracts and corpus callosum) and thalami. This observation, which is in
agreement with previous findings, indicates that diffusion abnormalities in the brains of patients with MS are present well beyond T2-visible lesions (7,24–27). NAWM damage has been repeatedly reported in patients with advanced stages of clinically definite MS (24–26,28–30). Furthermore, it is considered the key to understanding the mechanisms associated with the accumulation of MS disability (31). Nevertheless, few researchers have used DTI analysis of NAWM in the assessment of patients with CIS suggestive of MS, and those who have conducted studies that were based on either a region-of-interest approach (5) or a histogram approach (6,7). However, region-of-interest analysis is time consuming and poorly reproducible, while histogram analysis yields a global quantitative assessment of the whole WM but does not yield any information on the location of damage. By contrast, voxelwise analysis, which in this study was conducted with TBSS, can be used to objectively identify regions of FA abnormalities.

TBSS has already been validated as an effective way to evaluate FA in WM, not only in patients with clinically definite MS (9–11) but also in patients with numerous other diseases, such as schizophrenia (32), amyotrophic lateral sclerosis (33), epilepsy (34), Alzheimer disease, (35) and Friedrich ataxia (36). In patients with MS, the FA alteration yields a measurement of both demyelination and axonal loss (37), with one study in particular suggesting that loss of myelin per se is sufficient to reduce FA (22). Our findings suggest that WM damage is present extensively in the earliest phases of disease.

VBM is used to estimate, voxelwise, the presence of a difference in GM volume between groups of subjects. This technique is not biased to any particular structure; thus, it yields a thorough assessment of GM differences across the brain. The MS lesions cause a confounding effect on the segmentation phase of VBM analysis, and lesion masking has been proposed as a solution to this problem (17). In the current study, no significant volume difference was found between patients and control subjects in whole normalized GM, WM, cerebrospinal fluid, or brain parenchymal fraction values. The absence of any global GM volume reduction in our study is in accordance with results in the literature: In a consistent number of studies, researchers did not detect global GM atrophy in patients with CIS or early-stage MS at clinical onset (38–43). There was only one study in which researchers found a reduction in cortical thickness in patients with MS at clinical onset (44). Nevertheless, patients with early-stage MS or CIS have shown a progressive development of GM atrophy for at least 3 years after clinical onset, as shown by findings of a cross-sectional study (45,46) and a 3-year longitudinal study (47).

In our study, VBM analysis did not reveal any regional GM loss in the patient group when compared with the healthy control group. To our knowledge, VBM analysis in patients with CIS and early MS has been conducted in only two studies (38–40), the results of which are in complete accordance with ours in regard to the absence of regional differences in cortical volumes between patients and healthy control subjects. However, unlike the current study and the study performed by Ceccarelli et al.

### Table 1

**Regions of Reduced FA in Patients with CIS and Healthy Control Subjects**

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Size (voxels)</th>
<th>P Value</th>
<th>Side</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticospinal tract</td>
<td>7761</td>
<td>&lt;.001</td>
<td>R</td>
<td>6</td>
<td>42</td>
<td>2</td>
</tr>
<tr>
<td>Trunk of corpus callosum</td>
<td>6646</td>
<td>&lt;.001</td>
<td>NA</td>
<td>13</td>
<td>31</td>
<td>8</td>
</tr>
<tr>
<td>Superior longitudinal fasciculus</td>
<td>2494</td>
<td>&lt;.001</td>
<td>L</td>
<td>25</td>
<td>44</td>
<td>5</td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>1232</td>
<td>&lt;.001</td>
<td>R</td>
<td>18</td>
<td>27</td>
<td>3</td>
</tr>
<tr>
<td>Corticospinal tract</td>
<td>820</td>
<td>&lt;.001</td>
<td>L</td>
<td>10</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Tapetum/corona radiata</td>
<td>468</td>
<td>&lt;.001</td>
<td>L</td>
<td>9</td>
<td>56</td>
<td>17</td>
</tr>
<tr>
<td>Superior longitudinal fasciculus</td>
<td>448</td>
<td>&lt;.001</td>
<td>R</td>
<td>33</td>
<td>41</td>
<td>4</td>
</tr>
<tr>
<td>Arcuate fasciculus</td>
<td>441</td>
<td>&lt;.001</td>
<td>R</td>
<td>48</td>
<td>32</td>
<td>9</td>
</tr>
<tr>
<td>Arcuate fasciculus (supramarginal gyrus)</td>
<td>420</td>
<td>&lt;.001</td>
<td>L</td>
<td>32</td>
<td>21</td>
<td>9</td>
</tr>
<tr>
<td>Thalamus</td>
<td>342</td>
<td>&lt;.001</td>
<td>R</td>
<td>9</td>
<td>23</td>
<td>10</td>
</tr>
<tr>
<td>Superior temporal gyrus/inferior frontooccipital fasciculus</td>
<td>321</td>
<td>&lt;.001</td>
<td>R</td>
<td>42</td>
<td>42</td>
<td>8</td>
</tr>
<tr>
<td>Middle temporal gyrus/inferior frontooccipital fasciculus</td>
<td>212</td>
<td>&lt;.001</td>
<td>L</td>
<td>40</td>
<td>44</td>
<td>6</td>
</tr>
<tr>
<td>Middle temporal gyrus/inferior frontooccipital fasciculus</td>
<td>183</td>
<td>&lt;.001</td>
<td>R</td>
<td>51</td>
<td>27</td>
<td>14</td>
</tr>
<tr>
<td>Arcuate fasciculus (supramarginal gyrus)</td>
<td>155</td>
<td>&lt;.001</td>
<td>L</td>
<td>49</td>
<td>32</td>
<td>5</td>
</tr>
<tr>
<td>Thalamus</td>
<td>151</td>
<td>&lt;.001</td>
<td>L</td>
<td>10</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>High corticospinal tract, precentral gyrus, hand area</td>
<td>142</td>
<td>&lt;.001</td>
<td>R</td>
<td>30</td>
<td>18</td>
<td>47</td>
</tr>
<tr>
<td>High corticospinal tract, precentral gyrus, hand area</td>
<td>142</td>
<td>&lt;.001</td>
<td>L</td>
<td>30</td>
<td>20</td>
<td>45</td>
</tr>
<tr>
<td>WM of the inferior frontal gyrus</td>
<td>126</td>
<td>&lt;.001</td>
<td>R</td>
<td>27</td>
<td>43</td>
<td>6</td>
</tr>
<tr>
<td>WM of the middle temporal gyrus</td>
<td>116</td>
<td>&lt;.001</td>
<td>R</td>
<td>53</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>Middle cerebellar peduncle</td>
<td>114</td>
<td>&lt;.001</td>
<td>R</td>
<td>25</td>
<td>47</td>
<td>39</td>
</tr>
</tbody>
</table>

Note.—The 20 largest clusters of decreased FA in patients with CIS and healthy control subjects have been considered and presented in descending order of size. Z-max corresponds to MNI152 average brain coordinates of the maximum intensity point of the cluster.

* L = left, NA = not applicable, R = right.
cant
highlighted by TBSS were located in the NAWM and not merely within lesions.
the corticospinal tracts, corpus callosum, superior longitudinal fasciculi, and inferior longitudinal fasciculi.
compared with healthy control subjects. These regions are located in bilateral WM tracts, particularly in
bilateral decrease in regional FA in many WM fiber tracts of the whole brain of patients with MS when
skeleton mask (white). The red-orange colorscale represents the alpha level (1)
overlaid on the MNI152 average brain; shown together are the average lesion mask (blue) and the mean
control subjects (voxel level,
patients with CIS and 16 healthy control subjects. Clusters of reduced FA in patients compared with healthy
control subjects. These regions are located in bilateral WM tracts, particularly in

cortical tracts, corpus callosum, superior longitudinal fasciculi, and inferior longitudinal fasciculi. The
overlay of the significant map clusters on the mean lesion mask shows that most of the abnormalities
highlighted by TBSS were located in the NAWM and not merely within lesions.

Table 2

<table>
<thead>
<tr>
<th>Region</th>
<th>Patients with CIS</th>
<th>Healthy Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>GM (mL)</td>
<td>675.8 ± 70.8</td>
<td>677.3 ± 83.9</td>
</tr>
<tr>
<td>WM (mL)</td>
<td>440.2 ± 50.6</td>
<td>446.2 ± 51.4</td>
</tr>
<tr>
<td>CSF (mL)</td>
<td>253.2 ± 48.6</td>
<td>279.8 ± 82.6</td>
</tr>
<tr>
<td>BPF (mL)</td>
<td>0.81 ± 0.02</td>
<td>0.8 ± 0.05</td>
</tr>
</tbody>
</table>

Note.—Data are mean normalized segmented volumes ± standard deviations.

(40), Henry et al (38) found thalamic and hypothalamic GM atrophy in patients with CIS. Interestingly, we found a significant FA reduction in the thalami of patients when compared with that in control subjects; this points to the presence of subtle ultrastructural damage within this structure that has yet to be reflected by a decrease in volume.

In consideration of the fact that VBM analysis reflects differences in volume, these results do not allow us to exclude the possibility of an ultrastructural GM alteration. DTI-based analysis, on the other hand, reflects alterations of the brain structure. In our analysis, small foci of GM alteration in the thalami were demonstrated, while no significant DTI alterations in cortical structures were present; this finding is in accordance with the findings of other researchers (48,49).

The current study yielded a number of consistent findings. Our results support the hypothesis that GM damage is secondary to focal and diffuse WM abnormalities and may be secondary to WM alterations, such as those due to virtual hypoxia, glutamate excitotoxicity, and Wallerian degeneration (50). Extensive axonal transection and subsequent Wallerian and retrograde degeneration have been seen in the WM in the early phase of MS (51). Moreover, many studies have failed to reveal GM damage in patients with CIS and early-stage MS (39,40,43), whereas GM atrophy has been seen at follow-up (42,46). Our results are in agreement with those of Pulizzi et al (52), who found WM damage with DTI but did not find GM damage with MR spectroscopy. We assume that the extensive WM damage we detected in this population will subsequently affect subcortical and cortical structures, a process that takes time and therefore is not yet detectable in this cohort of patients with CIS. In fact, patients with a primary progressive form of MS who were studied with a similar method (10) had a widespread FA alteration already associated with GM loss. The hypothesis that GM and WM damage are independent factors (53) that occur at different times cannot, however, be ruled out by our results, and longitudinal studies on the same population are warranted to clarify this issue.

One limitation of this study was the use of a suboptimal DTI sequence, which used fewer diffusion-encoding gradient directions than other studies. Nevertheless, our article indicated that a different number of diffusion gradient directions lead to similar values of FA (54). Furthermore, our study was affected by all the limitations typical of VBM, such as its limited sensitivity and the need for spatial smoothing for GM analysis alone, which compromises its accuracy (55).

In conclusion, our results show that diffuse WM damage is detectable in patients with MS from the earliest stages of disease, when no significant changes can be observed in regional GM volumes; this suggests that GM damage is likely to be secondary to WM damage and is therefore not detectable in this phase in patients with CIS.

References


