IMPORTANCE The investigation of cortical gray matter (GM), deep GM nuclei, and spinal cord damage in patients with primary progressive multiple sclerosis (PP-MS) provides insights into the neurodegenerative process responsible for clinical progression of MS.

OBJECTIVE To investigate the association of magnetic resonance imaging measures of cortical, deep GM, and spinal cord damage and their effect on clinical disability.

DESIGN, SETTING, AND PARTICIPANTS Cross-sectional analysis of 26 patients with PP-MS (mean age, 50.9 years; range, 31-65 years; including 14 women) and 20 healthy control participants (mean age, 51.1 years; range, 34-63 years; including 11 women) enrolled at a single US institution. Clinical disability was measured with the Expanded Disability Status Scale, 9-Hole Peg Test, and 25-Foot Walking Test. We collected data from January 1, 2012, through December 31, 2013. Data analysis was performed from January 21 to April 10, 2015.

MAIN OUTCOMES AND MEASURES Cortical lesion burden, brain and deep GM volumes, spinal cord area and volume, and scores on the Expanded Disability Status Scale (score range, 0 to 10; higher scores indicate greater disability), 9-Hole Peg Test (measured in seconds; longer performance time indicates greater disability), and 25-Foot Walking Test (test covers 7.5 m; measured in seconds; longer performance time indicates greater disability).

RESULTS The 26 patients with PP-MS showed significantly smaller mean (SD) brain and spinal cord volumes than the 20 control group patients (normalized brain volume, 1377.81 [65.48] vs 1434.06 [53.67] cm³ [P = .003]; normalized white matter volume, 650.61 [46.38] vs 676.75 [37.02] cm³ [P = .045]; normalized gray matter volume, 727.20 [40.74] vs 757.31 [38.95] cm³ [P = .02]; normalized neocortical volume, 567.88 [85.55] vs 645.00 [42.84] cm³ [P = .001]; normalized spinal cord volume for C2-C5, 72.71 [7.89] vs 82.70 [7.83] mm³ [P < .001]; and normalized spinal cord volume for C2-C3, 64.86 [7.78] vs 72.26 [7.79] mm³ [P = .002]). The amount of damage in deep GM structures, especially with respect to the thalamus, was correlated with the number and volume of cortical lesions (mean [SD] thalamus volume, 8.89 [1.10] cm³; cortical lesion number, 12.6 [11.7]; cortical lesion volume, 0.65 [0.58] cm³; r = −0.52; P < .01). Thalamic atrophy also showed an association with cortical lesion count in the frontal cortex (mean [SD] thalamus volume, 8.89 [1.1] cm³; cortical lesion count in the frontal lobe, 5.0 [5.7]; r = −0.60; P < .01). No association was identified between magnetic resonance imaging measures of the brain and spinal cord damage.

CONCLUSIONS AND RELEVANCE In this study, the neurodegenerative process occurring in PP-MS appeared to spread across connected structures in the brain while proceeding independently in the spinal cord. These results support the relevance of anatomical connectivity for the propagation of MS damage in the PP phenotype.
Primary progressive multiple sclerosis (PP-MS) is characterized by the absence of exacerbation before clinical progression and by the presence of few macroscopic inflammatory brain lesions, marked cortical demyelination, diffuse white matter (WM) injury, and severe atrophy of cortical and subcortical gray matter (GM) and spinal cord. Cortical lesions are reported in as many as 80% of patients with PP-MS; and their detection and characterization has been improved by the application of newly implemented magnetic resonance imaging (MRI) sequences, such as double inversion recovery (DIR) and phase-sensitive inversion recovery (PSIR).

Similar to brain volume loss, deep GM (DGM) atrophy occurs at the early stages of the disease and preferentially involves the thalamus, where atrophy has been shown to be an important predictor of long-term disability in PP-MS. At later disease stages, however, the pathologic process spreads to other DGM structures, especially the caudate and putamen nuclei.

The spinal cord is a major site of involvement in PP-MS, with lesions being present in about 50% of the patients along with extensive spinal cord atrophy, which is considered a distinctive pathologic feature and a predictor of disability. Although extensive alterations of the spinal cord have been reported in PP-MS, whether this damage results only from local trauma and moderate to severe head trauma; (2) major hematological, renal, or hepatic dysfunction; (3) current or past Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) diagnosis of major depressive, bipolar, and psychotic disorders or substance abuse; and (4) contraindications to MRI. All enrolled participants underwent clinical evaluation and MRI on the same day. In the PP-MS group, disability assessment included the EDSS, 9-Hole Peg Test (9-HPT) (measured in seconds; longer performance time indicates greater disability), and 25-Foot Walking Test (test covers 7.5 m; measured in seconds; longer performance time indicates greater disability).

The study was approved by the institutional review board committee of Icahn School of Medicine at Mount Sinai, and written informed consent was obtained from all participants before investigation. Data were collected from January 1, 2012, through December 31, 2013.

**MRI Acquisition**

Magnetic resonance imaging was performed on a 3-T system (Achieva; Phillips Medical Systems) using an 8-channel SENSE receive-only head coil and a 16-channel receive-only neurovascular spine coil. Magnetic resonance imaging of the brain included the following sequences: (1) an axial dual-echo, turbo spin-echo sequence with a repetition time (TR) of 2500 milliseconds, echo times 1 and 2 (TE1/TE2) of 10/80 milliseconds, field of view of 230 × 230 mm², matrix size of 512 × 512, and 46 contiguous slices 3 mm thick; (2) a sagittal 3-dimensional, T1-weighted, turbo field echo sequence with a TR of 7.5 milliseconds, TE of 3.5 milliseconds, inversion time (TI) of 900 milliseconds, and a voxel size of 1 × 1 × 1 mm³; (3) an axial DIR with a TR of 11 000 milliseconds, TE of 25 milliseconds, and TI of 3400 milliseconds; and (4) an axial PSIR with a TR of 4500 milliseconds, TE of 8 milliseconds, and TI of 400 milliseconds. Double inversion recovery and PSIR were acquired with a field of view of 250 × 250 mm², matrix size of 256 × 256, 46 contiguous slices 3 mm thick, and a reconstructed spatial resolution of 0.5 × 0.5 × 3 mm³. Magnetic resonance imaging of the spinal cord included the following sequences: (1) a sagittal T2-weighted, turbo spin-echo sequence with a TR of 4097 milliseconds, TE of 120 milliseconds, a field of view of 250 × 250 mm², a matrix of 512 × 512, and 13 slices 3 mm thick and (2) a sagittal 3-dimensional, T1-weighted sequence with a TR of 8.10
milliseconds, TE of 4.60 milliseconds, TI of 1000 milliseconds, and voxel size of 1 × 1 × 1 mm³.

MRI Analysis
Brain Lesion Count and Volume
We defined T2-weighted hyperintense lesion volume and T1-weighted hypointense lesion volume with a semiautomated segmentation technique (DISPLAY, Montreal Neurological Institute [MNI]) as previously described. 30,31 Based on recent evidence that PSIR increases the accuracy of cortical lesion classification, 20,32 2 expert observers (M.P. and M.I.) identified and counted cortical lesions and segmented them on PSIR images in the PP-MS and control groups using DIR and T2-weighted images as references (Jim, version 6; Xinapse Systems).

Cortical lesions recognized on PSIR were classified according to published consensus criteria 9, 10, as intracortical (only involving GM), leuкоkortical (mixed GM and WM lesions), or juxta- cortical (only involving WM) depending on their location. From the intracortical and leuкоkortical GM lesions, cortical lesion masks were created and coregistered to the standard space (FMRIB software library [FSL]; FMRIB Centre) to assess the spatial distribution, number, and volume of cortical lesions across the different lobes (ie, frontal, parietal, temporal, and occipital; probabilistic MNI structural template atlas [http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases]), the motor cortex (primary motor cortex and premotor cortex; Jülich histological atlas [http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases]), and the somatosensory cortex (primary and secondary somatosensory cortex; Jülich histological atlas). 31 The same procedure was applied to the proton density-weighted images to assess the lesion count and volume in the DGM nuclei (ie, the thalamus, caudate, pallidum, and putamen) using the Harvard-Oxford subcortical structural atlas and implemented in FSLView as in Calabrese et al. 31

Brain Volumes
Normalized brain, WM, and GM volumes were measured on 3-dimensional T1-weighted images using SIENAX. 32 To avoid tissue misclassifications, the impact of WM lesions was corrected by filling the lesions with a distribution of signal-intensity values equivalent to those in normal-appearing WM in the image (lesions in-painting). 33 The normalized neocortical volume was measured by applying a standard space mask from FSL to the individual GM probability map from SIENAX. 34

Volume estimation for DGM structures (ie, the thalamus, caudate, pallidum, and putamen) was performed on 3-dimensional T1-weighted images using the FIRST method (implementation available with FSL; FMRIB Centre). 35 All segmented subcortical regions were visually checked for errors in registration and segmentation. The DGM volumes were normalized by multiplying the raw volumes by the SIENAX scaling factor. Because no statistically significant difference was detected between the right and left thalamus, caudate, putamen, and pallidus nuclei volumes (range of P values, >.30 to <.80), their value is reported as the mean between the 2 sides. 36

Spinal Cord
In patients and controls, the presence and number of spinal cord lesions was assessed on T2-weighted images by an experi-enced neuroradiologist. Spinal cord volume and cervical cord cross-sectional area were measured in patients and controls on the 3-dimensional T1-weighted image from C2 to C5 and from C2 to C3 using a semi-automatic segmentation method (Jim, version 6) as previously described (Figure 1). 37,38 To compensate for the biological variation unrelated to disease effects, spinal cord volume and cervical cord cross-sectional area were subsequently normalized as follows: spinal cord volume was divided by the number of slices (SVn), 39 and the mean cervical cord cross-sectional area was divided by the intracranial cross-sectional area (CSAn). 37

Statistical Analysis
Data analysis was performed from January 21 to April 10, 2015. Statistical evaluation was performed with SPSS software (version 20.0; IBM). The PP-MS and control groups were compared in terms of age and sex using a Mann-Whitney test and the Fisher exact test. An analysis of variance model with an a priori contrast was applied to investigate between-group comparisons. Bivariate correlations between MRI metrics for imaging of the brain and spine were evaluated using a Spearman correlation coefficient. Partial correlations between cortical lesions and DGM volumes were controlled for DGM lesion volume. For all data, statistical significance was set at P < .05. Unless otherwise indicated, data are expressed as mean (SD).

Results
We enrolled 26 patients with PP-MS (mean age, 50.9 years; range, 31-65 years; including 14 women [54%]) and 20 controls (mean age, 51.1 years; range, 34-63 years; including 11 women [55%]). No significant group differences were observed with regard to age (P = .60) or sex (P = .50). Mean duration of disease was 8.8 (4.6) years; median EDSS score, 4.0 (range, 1.5-6.0); mean 25-Foot Walking Test score, 7.3 (2.1) seconds; mean 9-HPT score for the dominant hand, 30.8 (11.6) seconds; and mean 9-HPT score for the nondominant hand, 37.4 (24.5) seconds. Twelve patients were receiving immunomodulatory treatment with glatiramer acetate (Copaxone), interferon beta-1a (Avonex and Rebif), or fingolimod (Gilenya).

Brain and Spinal Cord Lesions
Non-specific WM abnormalities on T2-weighted images were observed in 9 controls. The mean WM lesion load volumes in patients determined on T2- and T1-weighted images were 5.56 (7.41) and 2.96 (4.80) cm³, respectively. A total of 315 cortical lesions were identified, with 192 labeled as leuкоkortical; 44, as intracortical; and 79, as juxta- cortical. The juxta- cortical lesions, which involved only WM, were excluded from the analysis. The count, characteristics, and spatial distribution of the cortical lesions are summarized in Table 1.

Six patients presented with T2-weighted hyperintense lesions in the thalamus (mean number, 0.46 [0.90]; mean volume, 0.02 [0.05] cm³); 8 patients, in the putamen (mean number, 0.46 [0.76]; mean volume, 0.03 [0.07] cm³); and 11 patients, in the caudate (mean number, 1.34 [1.91]; mean volume, 0.17 [0.26] cm³). Twenty-three patients (88%) had at least 1 spinal...
cord lesion. No spinal cord lesions were detected in the controls. A higher lesion count in the spinal cord was associated with a smaller CSAn for C2 to C5 ($r = -0.39; P < .05$), SVn for C2 to C3 ($r = -0.49; P < .01$), and CSAn for C2 to C3 ($r = -0.56; P < .01$).

### Brain and Spinal Cord Volumes

Brain and spinal cord volumes for the PP-MS and control groups are reported in Table 2. Normalized brain, WM, GM, and neocortical volumes were significantly lower in patients compared with controls ($P = .003$, $P = .045$, $P = .02$, and $P = .001$, respectively), as were the volumes of the thalamus and putamen ($P < .001$ and $P = .02$, respectively). No significant differences were observed for the other DGM nuclei. The SVn and CSAn for C2 to C5 and C2 to C3 were significantly smaller in patients with PP-MS compared with controls ($P < .001$, $P = .002$, $P < .001$, and $P = .002$, respectively).

### Association Between DGM Volumes and Brain MRI Measures

All DGM nuclei volumes other than the globus pallidus showed a modest but significant positive correlation with normalized WM and brain volumes but not with the normalized neocortical volume (Table 3). Correlations between DGM volumes and cortical lesion number and volume are shown in Table 3. The volume of the thalamus was inversely correlated with the number ($r = -0.60; P < .01$) and volume ($r = -0.56; P < .01$) of cortical lesions in the frontal lobe (Figure 2).
Association Between Brain Measures and Spinal Cord
No statistically significant association was found between spinal cord volumes and areas and brain atrophy or lesion load. Specifically, we found no significant association between spinal cord atrophy and cortical lesion number or volume. The analysis had the same outcome when the cortical lesions were considered according to their spatial distribution in brain cortices and in the motor and somatosensory areas (Table 1).

Association Between MRI Findings and Clinical Measures of Disability
Although a modest association was present between the normalized brain and WM volumes with the 9-HPT score for the nondominant hand ($r = -0.35$ and $r = -0.37$, respectively), the association did not reach statistical significance. However, we found a modest but significant correlation between the T2-weighted hyperintense lesion volume and the 25-Foot Walking Test scores ($r = 0.39, P = .05$), whereas no correlations were detected between cortical lesion number and volume and clinical disability. The thalamic volume ($r = -0.48, P = .02$) and SVn for C2 to C5 ($r = -0.44, P = .03$) showed an inverse correlation with the 9-HPT score for the nondominant hand.

Discussion
Imaging and histopathologic studies have shown that GM injury in PP-MS is not limited to the neocortex but also involves the subcortical GM and the spinal cord. In line with these studies, our population of patients with PP-MS showed decreased brain, cortical, and subcortical GM volume and spinal cord atrophy. The link between the different pathogenic mechanisms leading to the development of the above-described pathologic alterations is still unknown, but (1) a common pathogenic process might affect different anatomical compartments simultaneously and/or (2) a pathogenic process initially may involve a specific compartment and spread to the anatomically connected structures over time.

Meningeal inflammation may serve as an example for a common pathogenic process affecting different anatomical compartments. A previous study has shown that, in patients with PP-MS, the presence of cortical lesions is linked to diffuse meningeal inflammation, implying that local factors produced by the inflammatory cells in the subarachnoid compartment have a crucial role in cortical lesion pathogenesis. Likewise, meningeal inflammation seems to be associated with diffuse axonal loss in the spinal cord and development of cord atrophy in PP-MS. We can speculate that a common soluble inflammatory factor, produced in the subarachnoid compartment and diffusing in the cere-
brospinal fluid, might be the trigger of the demyelinating process in the cortex and DGM and of the axonal loss in the spinal cord. The strong anatomical interconnection existing between DGM structures and the cerebral cortex and the projections from the spinal cord to the thalamus might represent a substrate for the propagation of pathologic alterations through anatomically connected structures. Both processes link the pathologic alterations affecting the cortex, DGM, and spinal cord, providing a theoretical background for the analysis of the association between structural abnormalities in these compartments.

In our population, we confirmed the association between normalized WM volume and DGM atrophy, which supports the role of WM atrophy as the relevant explanatory variable for DGM atrophy; in addition, our analysis revealed the presence of a correlation between DGM atrophy and cortical demyelination. The strength of this correlation was higher for the thalamus, followed by the putamen and caudate, and such a gradient in correlation strength replicates the extent of anatomical connection between these structures and the cortex. In addition, the volume of the globus pallidus, which does not have any direct connection with the cortex, did not show any correlation with cortical lesions, which reinforces the hypothesis of pathologic process spreading through anatomical patterns. Conversely, a strong association was found between thalamic volume and lesion burden in the frontal lobe, which is the cortical region that receives the highest number of projections from the thalamus. Although we cannot establish any causality between the presence of cortical lesions and thalamic atrophy, our results suggest that lesional cortical demyelination might influence the development of DGM atrophy.

We did not find any associations between spinal cord atrophy and cortical lesion count and volume, even when the regional analysis of cortical lesions across cortices and in the motor and somatosensory areas was taken into account, suggesting that a closer, more direct anatomical connection is required for the pathologic spreading or that the pathologic processes affecting the cortex and the spinal cord are independent of each other. Likewise, in line with previous findings, we did not find any association between the

### Table 3. Association Between DGM Volumes and Brain and Lesion MRI Measures

<table>
<thead>
<tr>
<th>DGM Volumes</th>
<th>Correlation</th>
<th>Brain Volumes, cm³</th>
<th>WM Lesion Volume, cm³</th>
<th>Cortical Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NBV</td>
<td>NWMV</td>
<td>NCV</td>
</tr>
<tr>
<td>Thalamus</td>
<td>0.48ᵇ</td>
<td>0.44ᵇ</td>
<td>0.18</td>
<td>−0.21</td>
</tr>
<tr>
<td>Putamen</td>
<td>0.52ᶜ</td>
<td>0.58ᶜ</td>
<td>0.53</td>
<td>−0.12</td>
</tr>
<tr>
<td>Caudate</td>
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<td>0.59ᶜ</td>
<td>0.63</td>
<td>−0.03</td>
</tr>
<tr>
<td>Pallidus</td>
<td>0.19</td>
<td>0.14</td>
<td>0.18</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Abbreviations: DGM, deep gray matter; MRI, magnetic resonance imaging; NBV, normalized brain volume; NCV, normalized neocortical volume; NWMV, normalized white matter (WM) volume; T1LV, T1-weighted hypointense lesion volume (LV); T2LV, T2-weighted hyperintense LV.

* All DGM volumes are calculated as the mean of the right and left sides and normalized. Correlations between the DGM and cortical lesions were corrected for DGM LVs.

³ P < .05.
⁴ P < .01.

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Figure 2. Partial Regression Plots Between Thalamic Volume and Frontal Lobe Cortical Lesions

The graph shows correlations between thalamic volume and the number and volume of cortical lesions in the frontal lobe controlled for thalamic lesion volume (LV). Thalamic volume constitutes the dependent variable; number and volume of cortical lesions, adjusted for thalamic LV, the independent variables. Axes represent residuals. Linear fit (middle line) and 95% individual CIs (upper and lower lines) are shown.
brain and cord volumes, suggesting that independent processes may result in differential rates of atrophy development in different compartments of the central nervous system. This conclusion is also supported by an extensive 5-year study on patients with PP-MS in which no correlation between progression of atrophy in the spinal cord and brain was observed.45

The lack of association between DGM and spinal cord volumes once again suggests the independence of the degenerative processes ongoing in the spinal cord and the brain. Although previous studies report contradictory findings regarding the association between T2 spinal cord lesions and development of cord atrophy in MS,16,23 in our population the correlation between the lesions in the spinal cord and the SVn and CSAn suggests that focal cord damage is a relevant contributor for the development of spinal cord atrophy in patients with PP-MS.

In contrast to previous studies20,21,38,46 we did not find any significant association between the EDSS score and spinal cord lesion load or atrophy in our patients with PP-MS. However, measures of ambulation ability and manual dexterity were affected by the amount of volume loss in the brain, thalamus, and upper cervical cord.21,38 This finding could be explained in part by the EDSS limitations, such as noninterval scaling, emphasis on ambulation status, reduced sensitivity in the middle and upper ranges of scores, and the absence of adequate cognitive and visual components, and/or the low sensitivity of the 9-HPT and 25-Foot Walking Test in patients with low levels of disability. Indeed, when the analysis was focused on the subgroup of patients with higher EDSS scores (>4.0), a significant association was found not only between the EDSS score and spinal cord volume but also between the 25-Foot Walking Test score and spinal cord volume, in agreement with the relevance of spinal cord atrophy for locomotor impairment and disability. Taken together, these results and the lack of association between spinal cord atrophy and disability in patients with a lower degree of disability46 support the concept that the effect of irreversible tissue loss in the spinal cord on disability becomes most prominent in more advanced stages of the disease.

Several limitations have to be considered when interpreting our results. First, the small sample size requires caution when interpreting the findings because the size may have affected our ability to reveal correlations between the MRI variables for the spine and brain and clinical data. Second, the acquired MRI protocol precluded the analysis of regional GM and WM cord volumes and the analysis of microstructural brain damage in selected WM tracts. Moreover, the low sensitivity in detecting associations between clinical impairment and MRI variables could be improved by the application of adapted clinical scales, reflecting disability in functions mediated by different anatomical pathways (ie, vibration perception threshold). Finally, the cross-sectional nature of our findings suggests but does not support any causal relationships among pathologic processes in different but connected anatomical structures. Future longitudinal studies in PP-MS that explore the association between macrostructural and microstructural brain GM damage, WM damage, and spinal cord atrophy of GM and WM since the early stage of the disease could help to elucidate the presence of a common degenerative mechanism or pathway involving different central nervous system structures.

Conclusions
We identified (1) a correlation between cortical demyelination and DGM atrophy that seems to reflect the pattern of anatomical connections between the 2 compartments and (2) an association between focal demyelination in the spinal cord and spinal cord atrophy. Therefore, we might infer that the neurodegenerative processes occurring in PP-MS involve simultaneously different anatomical compartments and seem to spread across connected structures in the brain while proceeding independently in the spinal cord.
Deep Gray Matter Damage in Primary Progressive Multiple Sclerosis

Original Investigation | Research

Biogen Idec, EMD Serono, Inc, Genentech, Genzyme Corporation, Novartis Pharmaceuticals Corp, Questcor Pharmaceuticals, and Teva Pharmaceutical Industries and participating in industry-sponsored nonpromotional, nonmarketing lectures for Genzyme Corporation and Biogen Idec. Dr Riley reported serving as a consultant and/or participant in advisory board meetings for Genzyme/Sanofi, Biogen Idec, Novartis Pharmaceuticals Corp, and Teva Pharmaceutical Industries and receiving research support from the National Multiple Sclerosis Society (NMSS). Dr Lublin reported receiving funding for research from Acorda Therapeutics, Inc, Biogen Idec, Novartis Pharmaceuticals Corp, Teva Neuroscience, Inc, Genzyme, Sanofi, Celgene, the National Institutes of Health (NIH), and NMSS; serving on consulting agreements, advisory boards, and data safety monitoring boards for Bayer Healthcare Pharmaceuticals, Biogen Idec, EMD Serono, Inc, Novartis Pharmaceuticals Corp, Teva Neuroscience, Inc, Acorda Therapeutics, Inc, Questcor Pharmaceuticals, Roche, Genentech, Celgene, Johnson & Johnson, and RevaNeuro; research support from a 2011 NINDS/NIH grant; serving as co-chief editor for Multiple Sclerosis and Related Disorders; and owning stock in Cognition Pharmaceuticals Inc. Dr Inglesè reported receiving research grants from the NIH, NMSS, Novartis Pharmaceuticals Corp, and Teva Neuroscience, Inc, and serving as a consultant for vaccine Inc. No other disclosures were reported.

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