Neocortical Atrophy, Third Ventricular Width, and Cognitive Dysfunction in Multiple Sclerosis

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Background: Cognitive dysfunction is common in multiple sclerosis (MS). Correlations are reported between atrophy and neuropsychological test results.

Objective: To determine if neocortical volume would supplant or supplement third ventricular width and other magnetic resonance imaging measures when predicting neuropsychological impairment.

Design: Cross-sectional study.

Setting: University MS clinic.

Participants: Seventy-seven patients with relapsing-remitting MS, 42 patients with secondary progressive MS, and 27 healthy control subjects.

Main Outcome Measures: Brain atrophy and lesion burden measures were obtained in all patients. A subset of 82 patients and all controls underwent neuropsychological testing.

Results: Patients with secondary progressive MS had more atrophy than patients with relapsing-remitting MS and controls. Neocortical volume was significantly correlated with all neuropsychological measures, with $r$ values ranging from 0.29 to 0.58. Third ventricular width was retained in most stepwise regression analyses predicting cognitive impairment in patients with MS and distinguishing secondary progressive from relapsing-remitting courses of MS.

Conclusions: We confirm an association between neocortical volume and multiple cognitive domains in MS, although neocortical volume did not explain significantly more variance than other magnetic resonance imaging measures. Of the magnetic resonance imaging variables studied, third ventricular width was retained in most regression models.

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Approximately 50% of patients with multiple sclerosis (MS) exhibit cognitive impairment that adversely affects employability and social skills. Research findings highlight the value of magnetic resonance (MR) imaging in predicting cognitive dysfunction in MS. Magnetization transfer ratio, whole brain atrophy, cortical atrophy, and lesion volume correlate with cognitive function. Arguably, the simple measure of third ventricular width (TVW) has shown the highest correlation with cognitive dysfunction compared with other MR imaging measures. In that study, TVW was significantly correlated with a wide range of tests measuring verbal memory, visuospatial memory, and processing speed; however, the regression models in the study would have been enhanced by newer semiautomated and automated MR imaging techniques that measure neocortical atrophy.

There is evidence of neocortical pathologic features in MS, but only 1 study has assessed the relationship between neocortical volume (NCV) and cognition, to our knowledge. That study showed significant correlation between NCV and measures of auditory and verbal memory, verbal fluency, and attention in 41 patients. In the present study, we aimed to replicate this work in a larger sample and to determine whether NCV would supplant or supplement TVW and other MR imaging measures in regression models predicting cognitive impairment.

METHODS

Subjects

Patients with MS (n = 119) provided informed consent and met diagnostic criteria for MS and for relapsing-remitting (RR) or secondary progressive (SP) disease. Exclusion criteria were
substance abuse, other current or past illness that could affect cognitive function, and MS relapse or corticosteroid use within the past 3 months. The mean±SD patient age was 44.6±8.5 years (age range, 24-65 years). The mean±SD number of years of education was 14.0±2.0 years (range, 10-18 years). Most patients (75%) were female, and 94% were white. The mean±SD disease duration was 12.2±8.2 years (range, 1-40 years). The median Expanded Disability Status Scale16 score was 3.5. There were 77 patients (65%) with RR MS and 42 patients (35%) with SP MS. A subset of 82 patients undergoing neuropsychological (NP) testing did not differ from untested patients on age, disease duration, years of education, or MR imaging findings by t test, except for somewhat higher normalized white matter volume among untested patients (t117=3.4, P<.01).

Healthy control subjects (n=27) had a mean±SD age of 44.0±9.0 years (age range, 24-58 years) and a mean±SD number of years of education of 14.6±2.2 years (range, 11-18 years). Most controls were female (81%) and white (89%). No significant demographic differences were found among the control, RR, and SP groups (P>.05). However, analysis of variance revealed a significant difference in age between controls and patients with SP MS (P<.05).

NP TESTING

Testing, based on a recent consensus report,17 was performed blinded to MR imaging findings. Verbal memory was assessed using learning and delayed recall indexes derived from the California Verbal Learning Test–Second Edition (CVLT-II).18 Visuospatial memory was assessed using analogous indexes from the Brief Visuospatial Memory Test–Revised (BVMT-R).19 Processing speed (or working memory) was assessed using total correct scores from the adaptations by Rao20 of the Paced Auditory Serial-Addition Task (PASAT)21 and the Symbol Digit Modalities Test (SDMT).22 These tests have good reliability and validity, as described in detail previously.9,23,24 Depression was assessed using the Beck Depression Inventory–Fast Screen,25 recently validated in MS.26

As in previous work,27 patients with MS were divided into cognitively impaired and cognitively intact groups. Tests were standardized using normative data from previously studied controls.27 Patients with scores at least 2 SDs below the control mean on one test and 1.5 SDs below the control mean on an additional measure were classified as being cognitively impaired. Patients were also considered cognitively impaired if they performed 1.5 SDs below the control means on 3 or more measures.

MR IMAGING PROTOCOL AND ANALYSIS

Patients underwent brain MR imaging using a 1.5-T whole-body MR imaging system (Signa 4X/LX; GE Medical Systems, Milwaukee, Wis). T2-weighted images, 3-dimensional T1-weighted spoiled gradient–recalled images, conventional spin-echo T1-weighted images, and fluid-attenuated inversion recovery images were obtained. Analysis was performed by operators (M.G.D., N.A., and S.H.) blinded to clinical characteristics and to NP test results. Lesion volumes were calculated using a reliable semiautomated contouring-thresholding technique for lesion segmentation, as previously described.6,20,24 For brain extraction and tissue seg-
mentation, we used the SIENAX (http://www.fmrib.ox.ac.uk\textbackslash{}analysis\textbackslash{}research\textbackslash{}siena/) cross-sectional brain atrophy analysis method (Figure 1). First, the brain extraction tool was used to remove all nonbrain and non–cerebrospinal fluid tissue from the image and to identify the outer surface of the skull. Brain and skull images were then used to perform a scaling-constrained registration to a standard brain and skull image set to determine a subject-specific normalization factor. The deskulled image was then processed using an automated image segmentation tool. Compartment-specific absolute volumes were then quantified by multiplying the outlined contouring method in which the volume was automatically calculated from the outlined regions by multiplying the outlined area by the section thickness. The mean coefficient of variation for LVV intrarater reproducibility was 0.53% (range, 0.27%-0.88%). Third ventricular width was measured via a line drawn through the long axis of the third ventricle, parallel to the interhemispheric fissure in the fluid-attenuated inversion recovery axial section where the third ventricle was most visible. The width (in millimeters) was measured by drawing a second line perpendicular to the first line at its midpoint. This procedure previously had a 2.4% coefficient of variation.

### STATISTICAL ANALYSIS

We compared the MS and control groups across MR imaging findings and NP test results using analysis of covariance (ANCOVA), controlling for demographic variables differing significantly between diagnostic groups. Pearson product moment correlation provided measures of relationships among MR imaging measures. Forward stepwise linear regression models (entrance criterion $P=0.05$ and exit criterion $P=0.10$) determined if disparate MR imaging predictors accounted for unique additive variance in NP functioning. Absolute values of statistically significant partial effect sizes were compared using Fisher exact test $r$ to $z$ score transformations. Finally, ANCOVA controlling for years of education was used to determine whether MR imaging measures would differentiate cognitively impaired and cognitively intact patients with MS. Analyses were conducted using SPSS for Windows version 13.0 (SPSS Inc, Chicago, Ill). Multiple regression and ANCOVA models were evaluated using standard procedures to ensure that final models met the underlying assumptions required by these statistical techniques. Significance for hypothesis-testing analyses was set at $P<.05$.

### RESULTS

Although there were no significant differences in sex, race/ethnicity, or years of educational achievement among the control, RR, and SP groups, analysis of variance revealed a significant difference in the groups’ ages (44.0±9.0, 42.9±7.6, and 47.7±9.2 years, respectively; $P=.01$). Tukey post hoc tests revealed that patients in the SP group were older than controls ($P<.05$). Consequently, age was used as a covariate for ANCOVA. Magnetic resonance imaging findings and NP test results were not significantly correlated with Beck Depression Inventory–Fast Screen scores. The mean values for the control, RR, and SP groups differed significantly for most dependent measures (Table 1).

### Table 1. Magnetic Resonance Imaging (MRI) and Neuropsychological (NP) Measures for the Control, Relapsing-Remitting (RR), and Secondary Progressive (SP) Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Group</th>
<th>RR Group</th>
<th>SP Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normalized MRI Measures</strong></td>
<td></td>
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<tr>
<td>White matter volume, mL</td>
<td>742.56 ± 48.23</td>
<td>719.79 ± 49.80</td>
<td>726.56 ± 54.49</td>
<td>.10</td>
</tr>
<tr>
<td>Gray matter volume, mL</td>
<td>786.00 ± 44.20</td>
<td>773.07 ± 59.21</td>
<td>702.82 ± 67.24‡</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Brain volume, mL</td>
<td>1528.46 ± 62.38</td>
<td>1492.87 ± 84.70†</td>
<td>1429.39 ± 87.21‡</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Neocortical volume, mL</td>
<td>592.12 ± 33.01</td>
<td>574.79 ± 47.83</td>
<td>522.42 ± 51.20‡</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lateral ventricular volume, mL</td>
<td>32.40 ± 11.05</td>
<td>41.67 ± 15.63‡</td>
<td>54.16 ± 21.24‡</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Third ventricular width, mm</td>
<td>2.23 ± 0.82</td>
<td>3.58 ± 3.83†</td>
<td>5.04 ± 3.83†</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>NP Measures</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>CVLT-II learning</td>
<td>56.81 ± 9.24</td>
<td>49.33 ± 8.84†</td>
<td>42.84 ± 14.09‡</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CVLT-II delayed recall</td>
<td>12.78 ± 2.29</td>
<td>10.65 ± 2.70†</td>
<td>8.52 ± 4.23†</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BVM-T-R learning</td>
<td>27.96 ± 5.39</td>
<td>21.58 ± 7.13†</td>
<td>17.16 ± 8.08†</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BVM-T-R delayed recall</td>
<td>10.67 ± 1.52</td>
<td>8.77 ± 2.78†</td>
<td>6.68 ± 3.44†</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PASAT</td>
<td>41.44 ± 11.11</td>
<td>35.53 ± 11.06‡</td>
<td>28.41 ± 16.18‡</td>
<td>.002</td>
</tr>
<tr>
<td>SDMT</td>
<td>62.85 ± 7.41</td>
<td>50.53 ± 12.03‡</td>
<td>40.40 ± 13.93‡</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BDI-FS</td>
<td>0.54 ± 1.03</td>
<td>4.04 ± 3.80†</td>
<td>3.12 ± 3.82†</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>


*Data are given as means±SD unless otherwise indicated.
†Significantly different from control group by Tukey post hoc test ($P<.05$).
‡Significantly different from control and RR group by Tukey post hoc test ($P<.05$).
In regression models controlling for age and years of education (Table 2), GMV (PASAT, PASAT r=0.47), NCV (BVMT-R r=0.31), and TVW (CVLT-II r=−0.40 and SDMT r=−0.62) accounted for most of the variance in predicting cognitive dysfunction. Brain volume (ΔR²=0.07, ΔF=10.64, P<.01) and TVW (ΔR²=0.33, ΔF=43.04, P<.001) were retained when predicting SDMT results. Age, years of education, BV, and TVW accounted for more than 51% of the variance in SDMT performance. There were no other significant additive stepwise regression models.

Analyses performed among the RR group only revealed no additive models. Third ventricular width was the sole predictor for SDMT results (ΔR²=0.19, ΔF=12.64, P<.01), and NCV was the sole predictor for PASAT results (ΔR²=0.15, ΔF=8.60, P<.01).

In the only additive models for the SP group, LVV (ΔR²=0.10, ΔF=5.84, P<.05) and TVW (ΔR²=0.19, ΔF=8.36, P<.01) were retained when predicting CVLT-II delayed recall. Brain volume was retained when predicting CVLT-II learning (ΔR²=0.16, ΔF=5.18, P<.05). Third ventricular width was the sole remaining predictor for PASAT results (ΔR²=0.20, ΔF=5.75, P<.05) and for SDMT results (ΔR²=0.38, ΔF=17.45, P<.001).

Except for white matter volume, retained atrophy measures failed to account for significantly more NP test result variance than atrophy measures removed from stepwise models. These findings were based on Fisher exact test results (data not shown).

Table 2. Stepwise Regression Analyses*

<table>
<thead>
<tr>
<th>NP Measure</th>
<th>Retained Magnetic Resonance Imaging Variables</th>
<th>Partial r for Retained Variable</th>
<th>Multiple R²</th>
<th>R² Change</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVLT-II learning</td>
<td>Third ventricular width</td>
<td>−0.34</td>
<td>0.26</td>
<td>0.10</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>CVLT-II recall</td>
<td>Third ventricular width</td>
<td>−0.40</td>
<td>0.30</td>
<td>0.14</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BVMT-R learning</td>
<td>Neocortical volume</td>
<td>0.30</td>
<td>0.14</td>
<td>0.07</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>BVMT-R recall</td>
<td>Neocortical volume</td>
<td>0.31</td>
<td>0.13</td>
<td>0.07</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>PASAT recall</td>
<td>Gray matter volume</td>
<td>0.47</td>
<td>0.27</td>
<td>0.21</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SDMT</td>
<td>Third ventricular width</td>
<td>−0.62</td>
<td>0.45</td>
<td>0.33</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Brain volume</td>
<td>0.58</td>
<td>0.52</td>
<td>0.07</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>


*Models were covaried by age and by years of education. All NP measures were included as predictor variables. The table gives final models predicting each NP measure, with only 1 additive model.

†R² change significance level.

Figure 2. Scatterplots demonstrating relationships between Symbol Digit Modalities Test (SDMT) results, neocortical volume (NCV), and third ventricular width (TVW) (1 outlier was excluded after examination of residuals revealed prediction of SDMT results >3.5 SDs and Cook's D=0.11). The dashed lines represent the regression lines for patients with secondary progressive (SP) multiple sclerosis (MS). The dotted lines represent the regression lines for patients with relapsing-remitting (RR) MS.

r=0.24, P=.03; and SDMT r=0.29, P=.01). Significant correlations and trends were also found between age and GMV (r=−0.31, P<.01), BV (r=−0.30, P<.01), NCV (r=−0.30, P<.01), LVV (r=0.19, P<.04), and TVW (r=0.18, P=.05). Neocortical volume was significantly correlated with all NP test results, with r values ranging from 0.29 (BVMT-R) to 0.58 (SDMT) (Figure 2).

In regression models controlling for age and years of education (Table 2), GMV (PASAT, PASAT r=0.47), NCV (BVMT-R r=0.31), and TVW (CVLT-II r=−0.40 and SDMT r=−0.62) accounted for most of the variance in predicting cognitive dysfunction. Brain volume (ΔR²=0.07, ΔF=10.64, P<.01) and TVW (ΔR²=0.33, ΔF=43.04, P<.001) were retained when predicting SDMT results. Age, years of education, BV, and TVW accounted for more than 51% of the variance in SDMT performance. There were no other significant additive stepwise regression models.
Table 3. Group Effects Comparing Cognitively Impaired and Cognitively Intact Patients*

<table>
<thead>
<tr>
<th>Normalized Magnetic Resonance Imaging Measure</th>
<th>Cognitively Intact Patients (n = 33)</th>
<th>Cognitively Impaired Patients (n = 49)</th>
<th>F Score</th>
<th>P Value</th>
<th>Cohen d</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1-weighted lesion volume, mL</td>
<td>1.47 ± 2.84</td>
<td>3.66 ± 4.91</td>
<td>3.99</td>
<td>.049</td>
<td>0.54</td>
</tr>
<tr>
<td>T2-weighted lesion volume, mL</td>
<td>9.18 ± 9.01</td>
<td>20.36 ± 20.00</td>
<td>8.61</td>
<td>.004</td>
<td>0.72</td>
</tr>
<tr>
<td>White matter volume, mL</td>
<td>713.13 ± 56.91</td>
<td>710.87 ± 50.73</td>
<td>0.005</td>
<td>.84</td>
<td>0.04</td>
</tr>
<tr>
<td>Gray matter volume, mL</td>
<td>786.18 ± 67.71</td>
<td>730.50 ± 72.94</td>
<td>12.51</td>
<td>.001</td>
<td>0.85</td>
</tr>
<tr>
<td>Brain volume, mL</td>
<td>1499.30 ± 88.68</td>
<td>1441.37 ± 98.11</td>
<td>6.53</td>
<td>.01</td>
<td>0.62</td>
</tr>
<tr>
<td>Neocortical volume, mL</td>
<td>584.86 ± 45.19</td>
<td>544.08 ± 57.95</td>
<td>10.51</td>
<td>.02</td>
<td>0.78</td>
</tr>
<tr>
<td>Lateral ventricular volume, mL</td>
<td>39.03 ± 14.63</td>
<td>50.87 ± 19.95</td>
<td>5.77</td>
<td>.02</td>
<td>0.68</td>
</tr>
<tr>
<td>Third ventricular width, mm</td>
<td>3.28 ± 1.76</td>
<td>4.72 ± 2.46</td>
<td>7.04</td>
<td>.01</td>
<td>0.67</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD unless otherwise indicated. The table gives statistical probabilities of group differences and effect sizes as indicated by Cohen d in which the difference between means is divided by the pooled SD.

The mean ± SD years of education were higher among cognitively intact patients (15.06 ± 1.84 years) than their cognitively impaired counterparts (13.22 ± 1.67 years) (t = 4.5, P < .01). Analysis of covariance (Table 3) revealed that these groups differed significantly on T2-weighted lesion volume, GMV, BV, NCV, LVV, and TVW.

Our findings confirm an association between NCV and cognition in MS. Neocortical volume was significantly correlated (P < .01) with all results of NP tests administered, and it differentiated cognitively impaired and cognitively intact patients. Consistent with previous research, the straightforward measure of TVW proved to be an equally valuable predictor of NP status. The third ventricle divides the thalamic hemispheres, and thalamic atrophy may give rise to ex vacuo enlargement of the third ventricle. However, regression analysis produced few additive models: no single MR imaging measure consistently showed statistical superiority when predicting cognitive performance.

Brain volume, LVV, and TVV differentiated the control, RR, and SP groups. Patients in the SP group exhibited more central atrophy than patients in the RR group, who in turn exhibited more central atrophy than controls. These findings suggest that measures of central atrophy may be better markers of MS-related degenerative change than lesion volume.

Cognitively intact patients had more years of education than cognitively impaired patients. Although the number of years of education was treated as a covariate, these data suggest that highly educated patients have more cognitive reserve, which could delay the onset of MS-related cognitive decline. Recent research has shown that cognitive activity can reduce cognitive decline among patients with Alzheimer disease. Such mental stimulation could stall the progression of mental decline in MS. Given the cross-sectional design of the present study, however, the issue of causality cannot be addressed herein.

A weakness of the present study is the lack of additional MR imaging measures with potential predictive power, including magnetization transfer imaging, diffusion tensor imaging, and MR imaging spectroscopy. These additional modalities measure microscopic cell damage, which cannot be captured by more traditional measures of lesion volume and atrophy. One or more of these measures may predict unique or additional variance in NP status among patients with MS. Another weakness is the cross-sectional design of the study. Because BV and NP status have been shown to vary over time, future research should use longitudinal designs that examine the predictive validity of the MR imaging measures investigated in this study. These concerns notwithstanding, the strengths of the study include our large sample of patients with MS and application of a comprehensive battery of reliable and well-validated measures of NP functioning. We conclude that central and cortical atrophy contribute equally to the development of cognitive dysfunction in MS.

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