Decreased Thickness of Primary Motor Cortex in Primary Lateral Sclerosis

**BACKGROUND AND PURPOSE:** Primary lateral sclerosis (PLS) is a rare form of motor neuron disease characterized by upper motor neuron dysfunction. Because pathologic examination has revealed a loss of neurons in the motor cortex of patients with PLS, we sought to confirm and extend this finding by using MR imaging to measure cortical thickness.

**METHODS:** Seven patients with PLS and 7 age-matched neurologically normal control subjects were examined with heavily T1-weighted short-$	au$ inversion recovery (STIR) MR imaging performed at 3T. Cortical thickness in the anterior and posterior banks of both the central and precentral sulci were measured.

**RESULTS:** Primary motor cortex (M1) was significantly thinner in patients with PLS than M1 in healthy control subjects, measuring $2.32 \pm 0.21$ mm compared with $2.79 \pm 0.18$ mm ($P = .0008$). Cortical thickness did not differ between the 2 groups for primary sensory cortex or for the anterior or posterior banks of the precentral sulcus. Therefore, loss of gray matter was specific to motor cortex. Although this difference was modest, cortical thickness discriminated between the 2 groups; only 1 PLS case was within the range of normal measurements.

**CONCLUSION:** Decreased thickness of M1 on the anterior bank of the precentral sulcus in patients with PLS, demonstrable by MR imaging, indicates a selective loss of upper motor neurons in this disease. Measurements of cortical thickness by MR imaging may provide a useful biomarker for diagnosis and study of upper motor neuron diseases.

**Methods**

**Study Population**
Seven patients (mean age, 52.9 ± 8.1 years) and 7 age- and sex-matched healthy control subjects (mean age, 53.4 ± 7.4 years) participated in the study (Table 1). All subjects were right-handed. All subjects gave written informed consent for the protocol, which was approved by the Institutional Review Board. The diagnosis of PLS was made using the working criteria proposed by Pringle et al. These criteria include clinical signs of corticospinal impairment without lower motor neuron loss, history of insidious progression, laboratory studies to exclude known etiology of progressive spasticity, and lack of family history. All 7 patients with PLS had impaired UMN function in all 4 extremities and bulbar regions, with a duration of disease of 7.9 ± 4.3 years. As an indication of the severity of impairment, finger tapping speed on a keyboard was measured for 3 15-second epochs with the use of a custom software program (LabView, National Instruments, Austin, Tex) and averaged for each hand. Control subjects had normal neurologic examinations and no history of neurologic or psychiatric disease.

**Imaging**
Imaging was performed on a 3T MR imaging system. In addition to routine brain imaging sequences, a high resolution STIR sequence...
computed and compared using MedCalc ver. 8.1 (MedCalc Software, Mariakerke, Belgium). Receiver operating characteristic curves were computed and compared using MedCalc ver. 8.1 (MedCalc Software, Mariakerke, Belgium). All values are reported as mean ± SD.

**Results**

Measurements of M1, S1, and the anterior and posterior banks of the pre-CS are summarized in Table 2. M1 in patients with PLS was significantly thinner than M1 in control subjects (Fig 2) (2.32 ± 0.21 versus 2.79 ± 0.18 mm; P = .0008). In contrast, no significant difference in cortical thickness between patients with PLS and control subjects was identified at S1 (1.49 ± 0.23 versus 1.34 ± 0.11 mm; P = .014), the anterior bank of the pre-CS (2.44 ± 0.19 mm versus 2.48 ± 0.15 mm; P = .68), or the posterior bank of the pre-CS (2.26 ± 0.18 mm versus 2.34 ± 0.12 mm, P = .33). M1 thickness discriminated between patients and control subjects with a high degree of sensitivity and specificity; the area under the ROC curve (AUC) was 0.94 ± 0.071.

To compensate for individual variation in cortical thickness, we performed 2 different normalizations (Table 2). First, we evaluated the ratio of cortical thickness across the CS; that is, we divided the thickness of M1 by that of S1. Using this normalization scheme, the M1/S1 normalized thickness of patients with PLS was still significantly reduced relative to control subjects (1.58 ± 0.22 versus 2.10 ± 0.28 mm, P = .020) but the level of significance was not as high (i.e., the P value was greater than before the normalization), and there was no change in the AUC of the ROC. The second normalization strategy was to divide the M1 thickness by the averaged thickness of the pre-CS banks. This normalization of M1 cortical thickness to the pre-CS cortices showed a significant difference in normalized M1 thickness (0.99 ± 0.04 versus 1.16 ± 0.06; P = .0005) but at a much higher level of significance (ie,
lower P value). A slight improvement in the separation of the 2 groups was seen with normalization (Fig 3), corresponding to an increase in the AUC of the ROC (AUC = 0.99). However, the 2 ROCs were not significantly different (P = .45).

No correlation between normalized cortical thickness and duration of disease was found ($R^2 = 0.1$). No correlation between cortical thickness and patient age was found ($R^2 = 0.05$). No correlation between cortical thickness and finger tapping rate was found ($R^2 = 0.004$).

No significant abnormalities were detected on clinical interpretation of the routine brain imaging. In particular, no focal signal intensity abnormalities were identified in the motor cortex or along the corticospinal tracts.

### Discussion

Assessment of UMN dysfunction is important in the characterization of motor neuron diseases such as ALS and PLS. Transcranial magnetic stimulation and MR spectroscopy are currently the methods most commonly used to assess the motor cortex in patients with PLS or ALS. Each method alone has a moderate sensitivity for detecting UMN abnormalities, with overlapping findings between patients and age-matched healthy control subjects. The combination of both measures has been advocated as a better means to diagnose UMN involvement in motor neuron disease, but additional imaging techniques may be another way to improve the detection of UMN abnormalities in ALS and PLS.

Pathologic studies suggest that at least some cases of PLS are characterized by a loss of Betz cells from M1. As regional thinning of the cortex has previously been demonstrated in other neurologic diseases, such as multiple sclerosis and Huntington disease, we focused our attention on a direct measurement of M1 cortical thickness. In our group of patients with PLS, all but 1 patient had a cortical thickness lower than the lowest value in the age-matched control subjects. Therefore, patients with PLS are characterized by a selective loss of gray matter in M1.

Primary motor cortex (M1) is readily identifiable on MR imaging by gross anatomic sulcal landmarks in most cases. Furthermore, the cytoarchitectonic distinction between M1 on the anterior bank of the CS and S1 on the posterior bank provides a reliable marker that is readily identified on MR imaging. Using a STIR sequence at 1.5 T, Meyer et al measured the thickness of the cortex on the anterior bank of the CS (M1) to be 2.70 mm and that of the posterior bank of the CS (S1) to be 1.76. In the current study, the thickness of M1, 2.79 mm, was quite comparable, but the thickness of S1, 1.34, was considerably smaller. For the banks of the pre-CS, our measure of 2.41 was also quite similar to that of Meyer et al of 2.47.

Several factors could account for the difference in the measurements of cortical thickness in the 2 studies. Higher field strength (3 T) alters the T1 relaxation rates of gray and white matter, providing a slightly different contrast in the current study than was obtained at 1.5T. Variations in the plane of section away from the intercommisural plane could introduce random error. The intercommisural plane, though nearly perpendicular to, is slightly oblique to the CS, so that some over-estimation of cortical thickness is likely in the absolute measurements for both studies and could result in systematic errors in cortical thickness. In contrast, the ratio of M1:S1 should be relatively resistant to changes in absolute thickness measurements due to section angulation. Perhaps most important is the difference in patient age; 56 years in this study compared with 31 years in that of Meyer et al. Finally, because S1 is quite thin and contrast is relatively poor, the error in measurement may be higher. This being said, it is interesting to note that our ratio of M1:S1 of 2.10 is close to the ratio of 2 reported by both Brodmann and von Economo and Koskinas. However, this variability in measurement is somewhat concerning, because using a specific pulse sequence and field strength limits the generalizability of the technique. It will be important to see whether these results will also be applicable to other high-resolution sequences that provide strong gray-white demarcation, such as magnetization-prepared rapid acquisition of gradient-echo, T1-fluid-attenuated inversion recovery, T1-fast-field echo, and fast echo spoiled gradient echo.

Many characteristics of the brain, including cortical thickness, vary with extrinsic factors such as age and sex. Therefore, some of the variability in the thickness data we measured could be attributable to such external variables. To a first ap-

### Table 2: Absolute and relative cortical thickness measurements in patients with PLS and control subjects

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<tr>
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<th>Control (mm)</th>
<th>PLS (mm)</th>
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<tbody>
<tr>
<td>Anterior</td>
<td>2.79 ± 0.18</td>
<td>2.32 ± 0.21</td>
</tr>
<tr>
<td>Pre-CS S1</td>
<td>1.34 ± 0.11</td>
<td>1.49 ± 0.23</td>
</tr>
<tr>
<td>Anterior</td>
<td>2.48 ± 0.15</td>
<td>2.44 ± 0.19</td>
</tr>
<tr>
<td>Posterior</td>
<td>2.34 ± 0.12</td>
<td>2.26 ± 0.18</td>
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<tr>
<th>M1 Ratios</th>
<th>M1:S1</th>
<th>M1:Pre-CS</th>
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<tbody>
<tr>
<td>Control</td>
<td>2.10 ± 0.28</td>
<td>1.16 ± 0.06</td>
</tr>
<tr>
<td>PLS</td>
<td>1.58 ± 0.22</td>
<td>0.99 ± 0.04</td>
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Note:—CS indicates central sulcus; M1, primary motor cortex; pre-CS, precentral sulcus; S1, primary sensory cortex.

Fig 2. Cortical thickness in patients with primary lateral sclerosis (PLS) versus control subjects. There is a significant reduction in cortical thickness in primary motor cortex (M1), but no difference in the other 3 cortices measured. +, significant at $P = .0008$; N.S., not significant; preCS, precentral sulcus; S1, primary sensory cortex.

of MR spectroscopy is relatively low, and we believe the data presented here by direct measurement of gray matter thickness to be more compelling evidence. Furthermore, the loss of UMs in motor cortex can explain the loss of corticospinal tract anisotropy, which has recently been demonstrated by diffusion tensor imaging.\(^6\)

Since the original description of PLS by Erb\(^{35}\) and Charcot and Joffroy\(^{36}\) more than 130 years ago, 19 autopsies of patients with PLS have been reported, only 6 of these since 1977. In 3 of these 6 cases, a loss of Betz cells from M1 was reported.\(^5,14,15\)

Reduced cortical thickness in PLS demonstrated by MR imaging is consistent with these pathologic studies. Furthermore, we found that reduced cortical thickness was the rule rather than the exception in this group of patients, indicating that loss of neurons in M1 may be an integral feature of PLS, extending the pathologic process beyond the lateral columns of the spinal cord.

Analysis of cortical thickness in M1 and adjacent frontal lobe may provide an ancillary test to confirm the diagnosis of PLS. However, we have only compared this measure with that of healthy age-matched control subjects. It will be important to extend this observation to other diseases that cause cortical atrophy (eg, frontotemporal dementia) and, more importantly, to disease processes that mimic PLS, particularly ALS. In addition, it will be important to extend this morphometric approach to the spinal cord and to examine the relationship between volume loss in the motor cortex and the gray and white matter compartments of the spinal cord.

Conclusions
Selective thinning of motor cortex can be demonstrated in patients with PLS. This is important for 2 reasons. First, it demonstrates that loss of UMNs in motor cortex occurs in PLS, as has been suggested by autopsy reports. Second, it shows that measuring cortical thickness may be a useful biomarker for the assessment of patients with motor neuron disease.

References
Primary lateral sclerosis and amyotrophic lateral sclerosis are different from amyotrophic lateral sclerosis.

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