Axonal Injury in the Internal Capsule Correlates With Motor Impairment After Stroke

S.T. Pendlebury, MRCP; A.M. Blamire, PhD; M.A. Lee, MRCP; P. Styles, DPhil; P.M. Matthews, DPhil

Background and Purpose—Magnetic resonance spectroscopy (MRS) in ischemic stroke has shown a correlation between N-acetylaspartate (NAA) loss from the infarcted region and disability. We tested the hypothesis that NAA loss in the descending motor pathways, measured at the level of the posterior limb of the internal capsule, would determine motor deficit after a cortical, subcortical, or striatocapsular stroke.

Methods—Eighteen patients with first ischemic stroke causing a motor deficit were examined between 1 month and 5 years after stroke. T2-weighted imaging of the brain and localized proton (voxel, 1.5×2×2 cm³) MRS from the posterior limb of each internal capsule were performed and correlated to a motor deficit score.

Results—Mean internal capsule NAA was significantly lower in the patient group as a whole compared with the control group (P<0.001). Reductions in internal capsule NAA on the side of the lesion were seen in cases of cortical stroke in which there was no extension of the stroke into the voxel as well as in cases of striatocapsular stroke involving the voxel region. There was a strong relationship between reduction in capsule NAA and contralateral motor deficit (log curve, r²=0.9, P<0.001).

Conclusions—Axonal injury in the descending motor pathways at the level of the internal capsule correlated with motor deficit in patients after stroke. This was the case for strokes directly involving the internal capsule and for strokes in the motor cortex and subcortex in which there was presumed anterograde axonal injury. (Stroke. 1999;30:956-962.)

Key Words: cerebrovascular disorders • nuclear magnetic resonance • outcome

In stroke, destruction of a given part of the brain causes a deficit of function. The type and severity of the deficit is determined by the magnitude of neuronal loss and the location of the lesion, together with the mitigating effects of adaptive recovery mechanisms. The development of MRI has enabled visualization of infarcts in the brain in vivo. However, lesion volume measured with T2 changes on MRI may not accurately assess neuronal damage, because lesions may be patchy and edema may contribute to T2 signal hyperintensity. Recently, magnetic resonance spectroscopy (MRS) has been used to attempt better quantification of the brain damage caused by stroke. Proton MRS allows in vivo measurement of N-acetyl–containing compounds, creatine, choline, and lactate. The majority of the N-acetyl signal comes from N-acetyl aspartate (NAA), which is present in high concentrations in the brain.¹ Much smaller contributions to the N-acetyl signal come from other N-acetyl groups, including N-acetylglutamate.² The function of NAA is unclear, although suggestions include initiation of protein synthesis, neurotransmission, and deactivation of glutamate. NAA is of particular interest in studies of the brain because it is located almost exclusively in neurons in the adult.³ Initially, it was suggested that decreases in NAA represented neuronal loss; recently, however, reversible decreases in NAA have been shown to occur in acute lesions in multiple sclerosis and in strokelike episodes in MELAS.⁵ Further, NAA synthesis in vitro has been shown to occur in an energy-dependent manner and to be reduced by mitochondrial inhibitors.⁶ Therefore, decreases in the NAA resonance peak in vivo must be interpreted as an index of neuronal or axonal injury rather than a marker of neuronal or axonal loss. Decreases in NAA have been shown to correlate with disability in multiple sclerosis,⁷ suggesting that axonal injury is responsible for chronic functional impairment in this disease.

Early studies of MRS in stroke showed increased lactate and decreased NAA within the stroke lesion.⁸–¹¹ Subsequently, attempts were made to determine whether the magnitude of neuronal damage as measured by NAA loss from the infarcted region, correlated with disability and impairment in stroke patients. Ford et al¹² found that the patients who made the most complete recoveries were those in whom NAA levels were relatively well preserved. In contrast, Gideon et al¹³ found no clear relationship between level of NAA and clinical outcome. Graham et al¹⁴ found that NAA reduction correlated with the Barthel Index score at discharge.
(a maximum of 5 weeks later in this study). This was recently corroborated by Federico et al., who found that NAA loss measured during the first week after stroke in patients with a speech or motor deficit correlated with the Scandinavian Stroke Scale and the Barthel Index at 6 months. The latter study suggests that MRS can be used to help predict which patients will do badly after stroke, but it remains unclear whether NAA loss is a better prognostic indicator than other factors, such as infarct volume as measured on imaging. Further, in all the studies of MRS and outcome after stroke outlined above, NAA loss was measured from the center of the infarcted region and thus was not representative of the total neuronal injury. Also, the NAA loss was not measured in a specific brain region directly relevant to the chosen outcome measures.

In our study using MRS, we aimed to examine the relationship between NAA loss after stroke and outcome in a specific functional system. We selected patients with a motor deficit secondary to a cortical, subcortical, or capsular stroke. NAA levels were measured in the posterior limb of the internal capsule containing the descending motor pathways and were correlated with motor impairment at the time of the MRS study. Our hypothesis was that the magnitude of axonal injury in the internal capsule would correlate with the motor deficit experienced by the patient. We proposed that this would be the case for striatocapsular strokes in which there was direct ischemic injury to the axons within the internal capsule and for cortical or subcortical strokes in which there was presumed Wallerian degeneration of the axons within the internal capsule.

**Subjects and Methods**

**Patients and Controls**

Eighteen patients (12 males, 6 females) who had suffered a stroke, as defined by the WHO criteria, between 1 month and 5 years before entry into the study that resulted in a motor deficit, were recruited from general practitioners and from the local stroke unit. Patients with hemorrhagic or brain stem stroke, history of prior symptomatic stroke, and other coexistent neurological disease or cognitive impairment were excluded from the study. Patients subsequently found to have >1 T2 hyperintense lesion on MRI consistent with infarction were not excluded from the study. Ten healthy control subjects of a similar mean age were recruited. The study was approved by the local ethics committee, and informed consent was obtained prior to the study.

**MRI and Spectroscopy**

MRI and spectroscopy were performed using a 2-T whole-body magnet interfaced with a Bruker Avance spectrometer (Bruker Medical). Care was taken to standardize head positioning across subjects by placing the subject’s head in a foam head localizer, with the orbitomeatal line positioned perpendicular to the long axis of the magnet. A forehead strap and side padding were used to immobilize the head. All images and spectra were obtained with a quadrature birdcage coil tuned to 85.2 MHz. A sagittal scout image was performed to confirm correct subject head alignment, followed by axial fast spin-echo T2-weighted imaging with the following parameters to provide 30 contiguous slices: TR=3100 ms, TE=82 ms, slice thickness=5 mm with nominal in-plane resolution of 1 mm, matrix=256×196 with zero filling=2562, field of view=25.6 cm, and averages=2.

Proton spectra were acquired from a 1.5×2×2 cm3 volume of interest (voxel) that was positioned visually on screen using the T2 axial images and was centered on the posterior limb of the internal capsule at the level of the third ventricle (Figure 1). Symmetrical placement of the voxel on the right and the left capsules was confirmed by 2 observers. Volume selection was performed with a point-resolved spectroscopy sequence (PRESS). Preliminary experiments on control subjects showed that a TE of 90 ms produced 20% more signal than the conventional TE of 135 ms, while minimizing problems arising from macromolecular resonances with very short T2 values. The other volume of interest acquisition parameters were TR=1500 ms, data points=2048, spectral width=2500 Hz, and acquisitions=256. Water suppression was produced using a chemical shift selection (CHESS) sequence. A non–water-suppressed spectrum was collected with 16 averages with no offset frequency from the same voxel.

The voxel dimensions were selected to include the whole of the posterior limb of the internal capsule with the minimum of partial volume effects. To avoid significant chemical shift displacement of the signal of interest (NAA), an offset frequency of −228 Hz relative to the water frequency was applied to all 3 pulses of the PRESS sequence. This ensured that the NAA signal was collected from precisely that volume of tissue enclosed by the voxel defined on the T2-weighted axial image. Spectral analysis was performed with the operator blinded to the patient’s clinical details and side of motor deficit. Four hertz of exponential line broadening was applied prior to Fourier transformation. Automatic line fitting and integration was done with the software package 1D WIN-NMR (Bruker Franzen Analytik GmbH).

The apparent NAA concentration was calculated relative to the water concentration for each internal capsule using the ratio of the areas under the NAA and water peaks were adjusted for differences in receiver gain and number of acquisitions but not for saturation effects. No attempt was made to perform a complete T1- and T2-compensated determination of the water peak, because the protocol was already at the limit of patient tolerance. However, the parallel increases in T1 and T2 relaxation times that are expected in chronic stroke will tend to self-compensate, making significant errors occurring as a result of T1 and T2 relaxation effects unlikely. Reduction in capsule NAA was calculated for each patient by taking the difference in apparent NAA concentration between the right and left capsules and expressing this as a percentage of the higher capsule NAA concentration. In patients in whom T2-weighted hyperintense regions were seen in both hemispheres, the same calculation was...
applied to obtain a measure of capsular NAA asymmetry. The mean, SD, and maximum of the difference in capsule NAA between sides in normal subjects as measured under our experimental conditions were obtained using the same method. Although changes in creatine and choline were seen in some of the patients, they were not analyzed in this study.

**Calculation of Lesion Volume**

Hyperintense regions seen on the T2-weighted axial scans were assumed to correspond to areas of infarction. Lesion area was measured in each patient with a manually defined thresholding technique (Medx Software, Sensor Systems). Lesion volume was calculated by multiplying the total lesion area by the slice thickness (5 mm). In those patients in whom the stroke was seen to involve the region enclosed by the voxel, the same manual thresholding technique was used to segment out the percentage of the voxel volume occupied by the stroke.

**Clinical Assessment**

Clinical assessment was carried out at the time of the MRS/MRI examination by a single observer (S.P.). Specific measures of motor function obtained from the patients were the Motricity Index, grip strength, 9-Hole Peg Test time, arm and leg extensor power compared with that of the unaffected limbs. A similar score was generated using the Barthel Index,23 which was used to obtain a measure of disability. Hand preference was assessed with the Salinas Hand Preference Index.24

**Data Analysis**

Mean internal capsule NAA was calculated for patients and controls using the average of the right and left internal capsule NAA concentrations for each subject. Comparisons were made between percentage reduction in internal capsule NAA and contralateral motor deficit score and Barthel score, respectively. In cases in which the NAA reduction was seen in the capsule ipsilateral to the motor deficit, the NAA reduction was given a negative value. Lesion volume was also compared with contralateral motor deficit. Comparison between percentage reduction in capsule NAA and ipsilateral lesion volume was made in patients in whom there was a single lesion on MRI (n = 12); patients with multiple lacunes were excluded from this analysis because it was not possible to determine which of the lesions lay within the motor outflow tract where they might have been expected to affect the NAA level in the descending motor pathways.

**Statistics**

Null hypotheses were tested using the Mann-Whitney U test. Correlations were tested with Spearman’s rank test. A curve-fitting approach was used to find the optimal description of the relationship between NAA reduction and motor deficit score (SPSS 7.5 for Windows, SPSS Inc).

**Results**

Clinical details for the patients are shown in Table 1. There was no significant difference between the mean ages of the patients and those of the control subjects (patients: 70.6 [range, 31 to 84] years; controls: 69.7 [range, 57 to 82] years).

Table 2 shows the MRS data and functional assessment scores for all the patients. NAA levels in the internal capsule in controls showed a mean ± SD difference of 9.2 ± 5.4% (range, 0% to 17%) between hemispheres. Mean internal capsule NAA was significantly lower in the patient group compared with the control group (40 ± 9 versus 51 ± 9; NAA/ H2O × 10−5, P = 0.009).

NAA loss from the internal capsule was associated with motor deficit. The relationship between NAA reduction and combined motor deficit score was better described by a log plot (r² = 0.89, P < 0.001; Figure 2) than other standard curves or a linear plot. There was a similar relationship between reduction in NAA and upper limb motor deficit score (log...
The relationship between motor deficit and NAA loss was significant whether patients were examined between 1 and 2.5 months or after 2.5 months poststroke. There was no significant relationship between reduction in NAA and Barthel Index score (Spearman $r = 0.3$, $P = 0.3$).

Seven patients (7, 9, 11, 12, 13, 16, and 18) showed a reduction in NAA in the internal capsule that exceeded the maximum right-left variation seen in control subjects. In each case, the reduced NAA level was seen on the side of the lesion, contralateral to the side of motor deficit. Reduction in NAA in the capsule ipsilateral to the motor deficit was seen in 5 patients (2, 3, 5, 6, and 10). None of these reductions was greater than control right-left capsule NAA differences.

Seven patients (1, 3, 4, 5, 6, 8, and 17) had lesions in both hemispheres, and in none of these patients were NAA reductions seen that were greater than control right-left differences. Of the 7 patients in whom there was reduced NAA on the side of the lesion, 3 (patients 7, 16, and 18) had strokes located primarily in the striatocapsular region enclosed by the spectroscopy voxel (mean percentage voxel volume occupied by T2 change, 50%; range, 28% to 70%).

### Table 2. Patient MRS, Functional Assessment, and Disability Data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Left Internal Capsule NAA*</th>
<th>Right Internal Capsule NAA*</th>
<th>Percentage Reduction in NAA†</th>
<th>% Voxels Occupied by Stroke, Left/Right</th>
<th>Motor Deficit/Affected Side</th>
<th>Upper Limb Motor Deficit/Affected Side</th>
<th>Barthel Index Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33</td>
<td>30</td>
<td>9</td>
<td>5/7</td>
<td>20/L</td>
<td>29/L</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>36</td>
<td>−16</td>
<td>17/0</td>
<td>8/L</td>
<td>16/L</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>51</td>
<td>−6</td>
<td>3/4</td>
<td>26/L</td>
<td>31/L</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>54</td>
<td>48</td>
<td>11</td>
<td>0/0</td>
<td>23/L</td>
<td>29/L</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>54</td>
<td>48</td>
<td>−11</td>
<td>1/0</td>
<td>9/R</td>
<td>8/R</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>36</td>
<td>−14</td>
<td>3/10</td>
<td>14/R</td>
<td>9/R</td>
<td>19</td>
</tr>
<tr>
<td>7</td>
<td>51</td>
<td>30</td>
<td>41</td>
<td>0/42</td>
<td>60/L</td>
<td>91/L</td>
<td>15</td>
</tr>
<tr>
<td>8</td>
<td>54</td>
<td>54</td>
<td>0</td>
<td>0/0</td>
<td>42/R</td>
<td>26/R</td>
<td>16</td>
</tr>
<tr>
<td>9</td>
<td>45</td>
<td>12</td>
<td>73</td>
<td>0/3</td>
<td>100/L</td>
<td>100/L</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>51</td>
<td>48</td>
<td>−6</td>
<td>0/0</td>
<td>34/R</td>
<td>35/R</td>
<td>18</td>
</tr>
<tr>
<td>11</td>
<td>27</td>
<td>45</td>
<td>40</td>
<td>9/0</td>
<td>71/R</td>
<td>94/R</td>
<td>17</td>
</tr>
<tr>
<td>12</td>
<td>42</td>
<td>21</td>
<td>50</td>
<td>0/14</td>
<td>93/L</td>
<td>100/L</td>
<td>9</td>
</tr>
<tr>
<td>13</td>
<td>0</td>
<td>54</td>
<td>100</td>
<td>38/0</td>
<td>93/R</td>
<td>94/R</td>
<td>7</td>
</tr>
<tr>
<td>14</td>
<td>45</td>
<td>48</td>
<td>6</td>
<td>0/0</td>
<td>70/R</td>
<td>82/R</td>
<td>14</td>
</tr>
<tr>
<td>15</td>
<td>42</td>
<td>48</td>
<td>13</td>
<td>0/0</td>
<td>44/R</td>
<td>64/R</td>
<td>20</td>
</tr>
<tr>
<td>16</td>
<td>51</td>
<td>12</td>
<td>76</td>
<td>0/51</td>
<td>74/L</td>
<td>91/L</td>
<td>20</td>
</tr>
<tr>
<td>17</td>
<td>45</td>
<td>45</td>
<td>0</td>
<td>4/2</td>
<td>31/L</td>
<td>29/L</td>
<td>20</td>
</tr>
<tr>
<td>18</td>
<td>0</td>
<td>48</td>
<td>100</td>
<td>70/0</td>
<td>77/R</td>
<td>91/R</td>
<td>19</td>
</tr>
</tbody>
</table>

*Expressed as the ratio of NAA to water (NAA/H2O × 10−5), not corrected for saturation effects.
†Difference between right and left internal capsule NAA levels expressed as a percentage of the higher capsule NAA level. Negative values indicate a reduction in capsule NAA ipsilateral to the motor deficit.

Figure 2. Percentage reduction in internal capsule NAA versus contralateral combined motor deficit score for all 18 stroke patients (log curve, $r^2 = 0.89$, $P < 0.001$). Filled squares indicate patients studied >2.5 months after stroke; open squares, patients studied <2.5 months after stroke.

Figure 3. Percentage reduction in internal capsule NAA versus contralateral combined upper limb motor deficit score for all 18 stroke patients (log curve, $r^2 = 0.91$, $P < 0.001$). Filled triangles indicate patients studied <2.5 months after stroke; open triangles, patients studied >2.5 months after stroke.
and 4 (patients 9, 11, 12, and 13) had strokes that were principally cortical or subcortical with little extension into the voxel region (mean percentage voxel volume occupied by T2 change, 16%; range, 3% to 38%). The percentage of the voxel volume occupied by stroke against reduction in NAA for these 7 patients is shown in Figure 4. The relationship between the extent of NAA reduction and motor deficit was similar regardless of the extent of T2 change seen within the voxel.

Lesion volume was significantly correlated with motor deficit (Spearman \(r = 0.7, P = 0.001\); Figure 5) and Barthel Index (Spearman \(r = 0.5, P = 0.03\)). Lesion volume was not significantly correlated with reduction in internal capsule NAA (all patients with a single lesion, \(n = 12\); Figure 6).

**Discussion**

Using MRS, we examined the relationship between axonal injury in the internal capsule, as shown by NAA loss, and functional impairment in patients who had suffered a motor stroke. There was a significant correlation between NAA loss in the capsule and motor deficit. These findings are consistent with the hypothesis that the extent of axonal injury in the descending motor pathways determines the magnitude of motor deficit in patients 1 month or more after stroke. In a recent study of multiple sclerosis patients with asymmetrical

impairment, Lee et al found a similar relationship between NAA loss in the internal capsule and motor deficit, although the correlation was not as strong as that observed in the present study of stroke patients. The lack of correlation we observed between axonal injury in the internal capsule and Barthel Index score can be explained by the fact that disability scales do not reflect damage to physiological systems as closely as impairment scales: patients will score well on the Barthel Index if they are independent in such activities as transferring from a wheel chair, regardless of the degree of limb weakness. We speculate that lesion volume correlated with Barthel score because larger infarcts are more likely to cause multiple problems, such as limb weakness, neglect, apraxia, and visual impairment, which contribute to disability.

Our study included patients with cortical, corona radiata, and striatocapsular strokes; hence, the extent of stroke extension, as shown by T2 change, into the region of the internal capsule enclosed by the spectroscopy voxel was highly variable (0% to 70%). In the 7 patients who had a reduction in capsule NAA greater than the maximum right-left difference seen in controls, the magnitude of the NAA reduction was independent of the amount of T2 lesion seen in the voxel. This is shown in Figure 4, where it can be seen that although there was a relationship between the percentage of the voxel volume occupied by stroke and the NAA reduction, in general the NAA loss was greater than would have been expected from the amount of lesion within the voxel. In particular, patients 7 and 13 had similar amounts of lesion within the voxel, but patient 13 had over twice the reduction in NAA. Similarly, patients 9 and 16 had similar levels of NAA loss, but the percentage of voxel volume occupied by stroke was 17 times higher in patient 16. Patients in whom NAA loss was closely related to the percentage of the voxel volume occupied by stroke (patients 7, 16, and 18) had strokes located principally in the striatocapsular region, whereas patients in whom the NAA loss was greater than that expected simply from the amount of T2 lesion within the voxel (patients 9, 11,
12, and 13) had cortical infarction. Thus, there were patients in whom the majority of axonal injury in the internal capsule within the voxel occurred as a result of direct involvement in the stroke and patients in whom significant damage to the axons in the internal capsule within the voxel must also have occurred as a result of anterograde degeneration. In other words, NAA loss was observed from normal-appearing white matter. Reduced NAA in normal-appearing white matter has also been shown to occur in patients with multiple sclerosis and head injury (M. Garnett, A.M. Blamire, and P. Styles, unpublished data, 1998). The time course of NAA loss from axons undergoing Wallerian degeneration is unclear and may be slower than NAA loss from the core of the infarct. It is possible that in the patients with cortical infarction, NAA losses from the internal capsule could have increased further after the study period.

Thus, NAA loss from the internal capsule would appear to provide a quantitative measure of functional axonal injury whether the injury occurs through direct ischemia to the axon within the spectroscopy voxel or through Wallerian degeneration. We did not see any of the characteristic imaging changes of Wallerian degeneration in our patients, but the imaging changes of Wallerian degeneration may not have been performed. Our results are in agreement with the finding that the extent of Wallerian degeneration after stroke as shown by T2-weighted imaging has been shown to be associated with severity of motor deficit. However, spectroscopic measurement of Wallerian degeneration would be expected to be more sensitive than measurement with T2-weighted imaging: not all patients show such imaging changes (estimates range from 45.8% to 100%), even in cases of severe motor deficit in which pathway degeneration must have occurred. Furthermore, the imaging changes of T2 hyperintensity in the degenerating pathways take 3 months to appear.

The strong relationship that we observed between reduction in internal capsule NAA and motor deficit suggests that recovery mechanisms after stroke are limited. This is supported by the observation that the plot of reduction in NAA versus motor deficit has a positive intercept. If large adaptive changes occurred after stroke, one would expect a negative intercept such that reductions in NAA in the capsule occurred in the absence of motor deficit. However, it is clear that some recovery is possible after stroke, and one proposed mechanism is that duplication of function in the descending pathways enables remaining intact pathways to take over from damaged ones. Pathway duplication may allow greater potential for recovery for coarse upper-limb function and leg function than for fine upper-limb movements that require integrity of the corticospinal tract from the contralateral hemisphere and cannot be controlled by the other descending pathways. This may explain in part why the curve for NAA reduction versus upper limb deficit is displaced to the left with respect to the curve for upper and lower limbs combined, indicating a greater upper-limb motor deficit for a given NAA reduction. Finally, it is possible that some of the acute deficit seen in stroke patients is secondary to potentially reversible metabolic compromise of neurons or axons. Resolution of this compromise could lead to patient recovery. Therefore, some of our patients, particularly those with minor deficits and no observable capsule NAA loss, may have had larger NAA losses acutely than were apparent at the time of the study.

The patients in our study were selected for motor deficit, and thus the infarcts would have involved the motor cortex or its projections in the subcortical white matter and internal capsule. Therefore, one might have expected an association between lesion volume and axonal injury in the capsule ipsilateral to the lesion. Lesion volume as measured by T2 changes on MRI was not correlated with capsule NAA loss when all patients with single lesions were included (n = 12) but was significant for patients with single lesions studied within 1 year of onset (n = 9, P = 0.03). The lack of correlation when more chronic patients were included could be explained by atrophy in the descending pathways causing the NAA loss to be underestimated (see below). It is of note that although lesion volume predicted contralateral motor deficit, the relationship was not as strong as that observed between NAA loss in the capsule and contralateral motor deficit.

There are a number of important points in our study relating to partial volume effects caused by the fact that the spectroscopy voxel included not only the descending motor pathways but also some basal ganglia and thalamus and the thalamocortical projections. First, partial volume effects may explain the fact that the relationship between NAA reduction and motor deficit is better described by a curve than by a linear plot. Assuming that the descending pathways occupy 60% of the voxel volume, a maximal motor deficit could result from a 60% NAA loss from the voxel region in cases where damage occurred exclusively to the motor pathways, sparing the other structures within the voxel. The graph of NAA reduction against upper limb deficit indicates that a maximal upper limb deficit occurs with a 40% NAA loss, which would be consistent with the fact that the upper limb motor pathways occupy a smaller volume within the voxel than all the motor pathways together.

Second, the partial volume effects could have resulted in insufficient sensitivity in our experiment to detect small NAA losses in the descending motor tracts in patients with minor strokes. Underestimation of NAA loss may also have occurred in the patients studied a year or more after stroke, owing to atrophy in the descending motor pathways. Histological and imaging studies have shown massive shrinkage in the midbrain, pons, and pyramids after hemispheric lesions causing hemiparesis. One patient, examined more than 2 years after stroke, had a large cortical lesion with moderate motor deficit but no NAA loss from the capsule on the side of the lesion. Atrophy of the damaged motor pathways in this patient may have caused the volume originally occupied by the damaged pathways to be replaced by the surrounding normal tissue, resulting in no measured loss of NAA signal from the voxel. Finally, the partial volume effects may have led to an overestimation of NAA loss in the descending motor pathways in patients with damage to the thalamus and basal ganglia as a result of direct ischemia, metabolic depression, or retrograde changes from cortical strokes. However, given the tight correlation observed between NAA reduction and motor deficit, it would seem that the partial volume effects described are not of major practical significance.
In conclusion, we have shown that axonal injury in the internal capsule, as measured by NAA loss, correlates with functional impairment in patients who have suffered a motor stroke. This was the case for cortical strokes in which there was presumed anterograde degeneration of the descending motor pathways passing through the capsule as well as for striatocapsular strokes in which there was direct involvement of the internal capsule in the stroke. MRS allows early assessment of axonal injury before T2-weighted imaging changes of Wallerian degeneration occur and provides a quantitative measure of damage. Future experiments should include longitudinal studies of patients after stroke to determine the time course of NAA loss in the internal capsule and whether there is a reversible component to this loss. This, together with monitoring of motor impairment, would allow assessment of MRS measurement of axonal injury in the internal capsule as a prognostic tool in patients after stroke.

Acknowledgments
Drs Pendlebury, Lee, and Matthews are supported by a Medical Research Council programme grant to Dr Matthews in the Centre for Functional MRI of the Brain, John Radcliffe Hospital, Oxford. Drs Blamire and Styles are also supported by the Medical Research Council.

References
Axonal Injury in the Internal Capsule Correlates With Motor Impairment After Stroke
S. T. Pendlebury, A. M. Blamire, M. A. Lee, P. Styles and P. M. Matthews

Stroke. 1999;30:956-962
doi: 10.1161/01.STR.30.5.956
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/30/5/956

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/