Relating MRI Changes to Motor Deficit After Ischemic Stroke by Segmentation of Functional Motor Pathways

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Background and Purpose—Infarct size on T2-weighted MRI correlates only modestly with outcome, particularly for small strokes. This may be largely because of differences in the locations of infarcts and consequently in the functional pathways that are damaged. To test this hypothesis quantitatively, we developed a “mask” of the corticospinal pathway to determine whether the extent of stroke intersection with the pathway would be more closely related to clinical motor deficit and axonal injury in the descending motor pathways than total stroke lesion volume.

Methods—Eighteen patients were studied ≥1 month after first ischemic stroke that caused a motor deficit by use of brain T2-weighted imaging, MR spectroscopic (MRS) measurements of the neuronal marker compound N-acetyl aspartate in the posterior limb of the internal capsule, and motor impairment and disability measures. A corticospinal mask based on neuroanatomic landmarks was generated from a subset of the MRI data. The maximum proportion of the cross-sectional area of this mask occupied by stroke was determined for each patient after all brain images were transformed into a common stereotaxic brain space.

Results—There was a significant linear relationship between the maximum proportional cross-sectional area of the corticospinal mask occupied by stroke and motor deficit ($r^2 = 0.82$, $P < 0.001$), whereas the relationship between the total stroke volume and motor deficit was better described by a cubic curve ($r^2 = 0.76$, $P < 0.001$). Inspection of the data plots showed that the total stroke volume discriminated poorly between smaller strokes with regard to the extent of associated motor deficit, whereas the maximum proportion of the mask cross-sectional area occupied by stroke appeared to be a more discriminatory marker of motor deficit and also N-acetyl aspartate reduction.

Conclusions—Segmentation of functional motor pathways on MRI allows estimation of the extent of damage specifically to that pathway by the stroke lesion. The extent of stroke intersection with the motor pathways was more linearly related to the magnitude of motor deficit than total lesion volume and appeared to be a better discriminator between small strokes with regard to motor deficit. This emphasizes the importance of the anatomic relationship of the infarct to local structures in determining functional impairment. Prospective studies are necessary to assess whether this approach would allow improved early estimation of prognosis after stroke. (Stroke. 2000;31:672-679.)

Key Words: brain ■ cerebrovascular disorders ■ magnetic resonance imaging ■ outcome ■ spectroscopy, nuclear magnetic resonance

Magnetic resonance techniques are becoming increasingly important for the evaluation of ischemic stroke. Conventional T2-weighted MRI visualizes infarcts of even a few millimeters across in the white matter or posterior fossa in subacute stroke. More recently, the technique of diffusion-weighted imaging, which generates contrast dependent on the diffusion of water molecules, has allowed visualization of infarcts as early as 2 hours after stroke and lesions as small as 4 mm in diameter.1–4

It is still unclear how best to relate imaging findings and functional outcome quantitatively to understand the mechanisms of impairment and determine prognosis. Previous studies have examined the relationship between stroke size and clinical outcome. Studies using computed tomography to measure lesion size5–8 have shown conflicting results. The largest such study4 found only a modest correlation ($r^2 = 0.3$) between subacute infarct volume and the National Institutes of Health Stroke Scale (NIHSS) at 3 months. In addition, although patients with large infarcts tended to have a poor outcome, the functional consequences of more moderate-size infarcts were more difficult to predict.

T2-weighted MRI is more sensitive than CT at detecting infarction9 and thus might be somewhat better at predicting outcome. In the only study known to us that looks specifically

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at T2-weighted MRI and outcome, Saunders et al.\textsuperscript{10} found that patients who were independent at 3 months had smaller strokes on MRI than patients who were dependent or dead. However, there was considerable overlap between infarct sizes in the 3 groups, and the outcome measures were rather coarse. One of the major reasons why outcome may not be correlated strongly with lesion volume is that volume measures do not take account of variations in lesion location or shape. In addition, T2-weighted MRI or CT changes provide relatively nonspecific measures of pathological change.

Recently, MR spectroscopy (MRS) has been used to further characterize the damage that occurs as a result of stroke. MRS allows measurement of N-acetyl aspartate (NAA), a chemical found almost exclusively in neurons,\textsuperscript{11} decreases in which have been proposed as an index of axonal or neuronal damage. NAA loss in a specific functional pathway, the descending motor tracts, has been shown to correlate strongly with motor impairment\textsuperscript{12} after stroke, illustrating that the clinical consequences of an ischemic lesion can be predicted if damage and outcome are measured within a specific functional system. However, MRS techniques have limitations in that they are not widely available, are time-consuming, and have limited spatial resolution.

Recently, Riahi and colleagues\textsuperscript{13} demonstrated in multiple sclerosis patients that measurement of lesion volumes within a corticospinal tract mask correlated more strongly with motor impairment than did total white matter lesion load. This was interpreted as indicating that the extent of damage specifically within the corticospinal tract is a major determinant of motor disability. However, the heterogeneous pathology of T2-weighted lesions in multiple sclerosis and the presence of abnormalities in the normal-appearing white matter complicates interpretation of the relationship between lesion volume and functional pathway localization in this disease.

In the present study, we applied an approach similar to that described by Riahi et al to the problem of relating ischemic stroke lesion volume to functional motor deficit. We chose motor impairment as our main outcome measure rather than stroke lesion volume to functional motor deficit. We chose MRI consistent with infarction were not excluded from the study. Patients subsequently found to have >1 T2 hyperintense lesion on MRI consistent with infarction were not excluded from the study.

Assessment of Motor Impairment
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,\textsuperscript{14} the 9-hole peg test,\textsuperscript{16} grip strength as measured by a modified strain gauge,\textsuperscript{17} and leg extension power as measured with a leg extensor rig dynamometer. A composite motor deficit score was generated by calculating the mean of the percentage performance of the affected arm and leg for motricity index, grip strength, 9-hole peg test time, and leg extensor power compared with the unaffected limbs. Thus, a complete hemiparesis with no function in the arm or leg gave a combined motor deficit score of 100. A similar score was generated from the tests of upper limb function alone (motricity index, grip strength, and 9-hole peg test). The Barthel Index\textsuperscript{18} was used to obtain a measure of disability.

MRI and MRS
MRI and MR spectroscopy (MRS) were performed with a 2-T whole-body magnet interfaced with a Bruker Avance spectrometer (Bruker Medical) as described previously.\textsuperscript{12} Briefly, images and spectra were obtained with a quadrature birdcage coil tuned to 85.2 MHz. A sagittal scout image was performed, 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=256,\textsuperscript{2} field of view=25.6 cm, and averages=2.

Proton spectra were acquired from a 1.5×2×2-cm\textsuperscript{3} volume of interest (voxel) positioned over the posterior limb of the internal capsule at the level of the third ventricle. Volume selection was performed with a point-resolved spectroscopy sequence (PRESS).\textsuperscript{19} The volume of interest acquisition parameters were TE=90 ms, TR=1500 ms, data points=2048, spectral width=2500 Hz, and acquisitions=256. Water suppression was produced with a chemical shift–selective\textsuperscript{20} sequence. A non–water-suppressed spectrum was collected from the same voxel with 16 averages and no offset frequency. Spectral analysis was performed with the operator blinded to the patient’s clinical details and side of motor deficit. A 4-Hz exponential line broadening was applied before Fourier transformation. Automatic line fitting and integration were done with the software package 1D WIN-NMR (Bruker Franzenz Analytik GmbH).

The apparent NAA concentration was calculated relative to the water concentration for each internal capsule by use of the ratio of the areas under the NAA and water peaks adjusted for differences in receiver gain and number of acquisitions but not for saturation effects. 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. Although changes in creatine and choline were seen in some of the patients, these were not analyzed in this study.

Subjects and Methods

Subjects
The data reported here were obtained from the same cohort of patients as included in the previous study relating axonal injury in the internal capsule and motor deficit.\textsuperscript{15} Eighteen patients (12 men, 6 women) who had suffered a stroke, as defined by the WHO criteria,\textsuperscript{14} resulting in a motor deficit between 1 month and 5 years before entry into the study were recruited from general practitioners and from the local stroke unit. Patients with hemorrhagic or brain stem stroke, history of prior symptomatic stroke, 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.

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 by 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).
Although patients who had had other volumes had values of 0. Figure 2 shows the intersection (so that volumes in both the mask and stroke had values of 1 and 0 outside. The binary image of each patient's stroke was transformed to the average brain by use of AIR. The binary mask was converted into a probabilistic mask by taking the 95% confidence interval of the standard mask. The probabilistic mask was transformed into a binary mask with values of 1 inside the mask and 0 outside. Figure 1 shows the mask in coronal, axial, and sagittal views.

By use of DISPLAY software (Montreal Neurology Institute, www.bic.mni.mcgill.ca/software/display/display.html), the selected region was colored to create an individual mask of the descending pathways for that hemisphere. Each hemisphere then was registered (automated image registration, AIR) to a standard brain template (MN1305 template, Montreal Neurology Institute), and the transformation algorithms were used to warp each mask into the mean brain space. All masks (right and left) were coregistered, and their borders were smoothed with a gaussian kernel of 7 mm full-width half-maximum). The resulting standard mask (corticospinal mask) was converted into a probabilistic mask by taking the 95% confidence interval of the standard mask. The probabilistic mask was transformed into a binary mask with values of 1 inside the mask and 0 outside. Figure 1 shows the mask in coronal, axial, and sagittal views.

Generation of the Average Brain Corticospinal Mask
From the T2-weighted images, 10 hemispheres from the unaffected side of 10 of the patients were selected at random. MEDx software (Sensor Systems) was used to display the images and create the mask. In each of the 10 hemispheres, the descending motor tracts were outlined as follows. The precentral gyrus was localized according to its neuroanatomic landmarks with the help of an atlas of the brain and was tracked superiorly to the vertex and inferiorly as far as the sylvian fissure. The white matter tracts descending from the precentral gyrus were tracked through the deep white matter to the posterior limb of the internal capsule, which was followed to the midbrain. Because the exact course of the corticospinal fibers from the precentral gyrus to the posterior limb of the internal capsule cannot be precisely determined from an MRI scan in any 1 individual, the most direct course between the precentral gyrus and the posterior limb was taken.

By use of DISPLAY software (Montreal Neurology Institute, www.bic.mni.mcgill.ca/software/display/display.html), the selected region was colored to create an individual mask of the descending pathways for that hemisphere. Each hemisphere then was registered (automated image registration, AIR) to a standard brain template (MN1305 template, Montreal Neurology Institute), and the transformation algorithms were used to warp each mask into the mean brain space. All masks (right and left) were coregistered, and their borders were smoothed with a gaussian kernel of 7 mm full-width half-maximum). The resulting standard mask (corticospinal mask) was converted into a probabilistic mask by taking the 95% confidence interval of the standard mask. The probabilistic mask was transformed into a binary mask with values of 1 inside the mask and 0 outside. Figure 1 shows the mask in coronal, axial, and sagittal views.

Measurement of the Maximum Cross-Sectional Area of Lesion Intersection With the Corticospinal Mask
On each patient’s T2-weighted MRI, the stroke was outlined by a manually defined thresholding technique (MEDx, Sensor Systems, Inc). A binary image of the stroke was created with values of 1 inside the stroke and 0 outside. The binary image of each patient’s stroke was transformed to the average brain by use of AIR. The binary stroke image was then multiplied by the corticospinal mask to determine the points of intersection between the stroke and the mask (so that volumes in both the mask and stroke had values of 1 and other volumes had values of 0). Figure 2 shows the intersection between a stroke lesion and the corticospinal mask.

Data Analysis
Although patients who had had >1 stroke according to the WHO criteria were excluded from the study, it was apparent in analysis of the results of the T2-weighted scans that several patients had >1 T2 hyperintense lesions and that these were often bilateral. Therefore, for comparisons between lesion volume and motor deficit and between lesion volume and percentage reduction in internal capsule NAA, the total lesion volume in the hemisphere contralateral to the motor deficit was used. In cases in which the NAA reduction was seen in the capsule ipsilateral to the motor deficit, the NAA reduction was assigned a negative value.

For comparisons involving the intersection of the stroke with the mask, the maximum proportion of the mask cross-sectional area (in the axial plane) occupied by stroke was calculated. Values for the maximum proportion of the mask cross-sectional area occupied by stroke could thus range from 0 (no stroke intersection with the mask) to 1 (cross-sectional area of the mask completely occupied by stroke lesion at some point in the axial plane).

Statistical Analysis
The distributions of the data on total stroke volume and maximum proportion of the mask cross-sectional area occupied by stroke were assessed by kurtosis tests to determine how far the distribution of values differed from that of a normal distribution. In addition, histograms were plotted in which cases were divided into deciles of the total range in values.

To find the best description of the relationships in data plots, a curve-fitting approach was applied (SPSS for Windows 7.5). Correlations were tested by Spearman’s rank test.

Results
The Table shows the clinical and MR data for all the patients. For the group of patients as a whole, the mean combined motor deficit score was 49.4±30.8 U (mean±SD), and the mean T2-weighted lesion volume was 41.7±47.4 cm³ (mean±SD).

The total lesion volume is plotted against the maximum proportion of the mask cross-sectional area occupied by stroke in Figure 3. This illustrates that large lesions occupied a consistently large proportion of the mask cross-sectional area, whereas smaller lesions showed greater variability in the amount of intersection with the mask. The distribution of values for the total stroke volume was skewed toward small values (mean 42 cm³, SD 47 cm³; kurtosis statistic −0.7, SE 1.04), whereas the distribution of values for the maximum proportion of the mask cross-sectional area occupied by stroke was more normally distributed (mean 0.37, SD 0.29; kurtosis −1.4, SE 1.04). Use of the maximum proportion of the mask cross-sectional area occupied by stroke discriminated better between strokes than did the total stroke volume,
especially for small strokes, as illustrated by the histograms in Figure 4. Although the numbers of cases were too small to allow formal assessment of statistical difference in distribution between the 2 populations, the histograms showed that whereas >44% of cases fell inside the first decile when stroke volume was measured, only just over 20% of cases fell inside the first decile when the maximum proportion of mask cross-sectional area occupied by stroke was used. Further-

![Figure 2. Axial MR slices showing the intersection of a stroke with the corticospinal mask from which the maximum proportion of the mask cross-sectional area occupied by stroke is calculated. The corticospinal mask is shown in dark gray, the stroke in light gray, and the point of intersection between the stroke and the mask in white.](image)

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<th>Patient</th>
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<th>Stroke Volume, cm³</th>
<th>Stroke Location on MRI/Hemisphere</th>
<th>Cross-Sectional Area of Mask Occupied by Stroke†</th>
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*
Volume of stroke in the hemisphere contralateral to the motor deficit.
†Maximum proportion of the cross-sectional area of the mask occupied by stroke.
‡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 internal capsule NAA ipsilateral to the motor deficit.
more, the latter measurement produced a more even distribution of cases throughout the range of deciles.

The relationships between total stroke volume and motor impairment ($r^2=0.76$, $P<0.001$) and between total stroke volume and NAA reduction in the internal capsule were best described by cubic plots ($r^2=0.76$, $P<0.001$) (Figure 5a and 5b). The relationships of the maximum proportion of the mask cross-sectional area occupied by stroke to motor deficit ($r^2=0.82$, $P<0.001$) (Figure 5c) and to NAA decrease in the posterior limb of the internal capsule ($r^2=0.84$, $P<0.001$) (Figure 5d) were described equally well by linear plots and by cubic plots. Inspection of the data plots showed that the maximum proportion of the mask cross-sectional area occupied by stroke discriminated between smaller strokes with regard to motor deficit and NAA decrease better than did the total stroke volume, resulting in more linear relationships.

There were only weak correlations between total stroke volume and Barthel Index (Spearman, $r^2=0.3$, $P=0.03$) and between the maximum proportion of the mask cross-sectional area occupied by stroke and Barthel Index (Spearman, $r^2=0.3$, $P=0.03$) (Figure 6a and 6b).

**Discussion**

We used a corticospinal mask to estimate the extent of stroke intersection with the corticospinal motor pathway. The maximum proportion of mask cross-sectional area occupied by stroke discriminated better between small strokes than did total stroke volume, resulting in a population distribution that was less skewed toward small values. As a result, the maximum proportional cross-sectional area of the mask occupied by stroke showed a more linear relationship to motor deficit and axonal injury in the corticospinal tract (as measured by NAA loss from the internal capsule) than did the total stroke volume. Similarly, the relationship between the maximum cross-sectional area of the mask occupied by stroke and percentage NAA reduction was more linear than the relationship between the total stroke volume and the percentage NAA reduction.

Our results showing a relationship between total stroke volume and functional impairment (or, less strongly, disability) are in agreement with previous studies. These studies have measured outcome at a variety of time points and with a range of outcome measures by both correlational and categorical analysis. It should be noted that the relationship between stroke size and outcome will be affected by these various factors, making quantitative comparisons between studies difficult. In particular, our primary functional measure was specific for motor impairment, whereas measures used in other studies have been broader and have tended to be biased toward assessments of global disability. In the study most comparable to ours, Lovblad et al showed a correlation ($r^2=0.4$) between T2-weighted infarct size and NIHSS at a median of 8 weeks after stroke. The correlation increased ($r^2=0.8$) when only the cortical infarcts were included. Therefore, these authors suggested that lesion location must be an important factor determining the outcome particularly from small strokes. Data from other studies confirm that although large strokes do badly, more moderate-size strokes have a more variable outcome.

We were unable to demonstrate a statistically significant superiority of the maximum proportion of the mask cross-sectional area occupied by stroke over the total stroke volume in determining motor deficit, possibly owing to the small number of subjects in the study. However, the data provide evidence that the maximum proportion of the mask cross-sectional area occupied by stroke may be a more sensitive and discriminatory measure than the total stroke volume, particularly for small strokes, with regard to the associated motor deficit and NAA reduction. Histogram plots revealed that the measure of cross-sectional area of the mask occupied by stroke...
stroke discriminated better between small strokes than did the total stroke volume, resulting in a more normally distributed population. The maximum cross-sectional area of the mask occupied by stroke in the axial plane had a linear relationship with motor deficit and NAA reduction, whereas the relationship between the total stroke volume and motor deficit did not. Visual inspection of the data showed that the nonlinearity of the relationship between the total stroke volume and motor deficit was caused by the wide range in motor deficits associated with smaller strokes, causing clumping of values along the y axis. This was not seen in the plot of the cross-sectional area of the mask occupied by stroke and motor deficit. Similarly, the maximum proportion of the mask cross-sectional area occupied by stroke had a more linear relationship to NAA reduction than did the total stroke volume. Taken together, the data suggest that the maximum proportion of the mask cross-sectional area occupied by stroke is a more discriminatory measure for associated motor deficit and axonal injury in the descending motor pathways than is the total stroke volume and that this is particularly the case for small strokes.

The results from this study support the hypothesis that both the location and the shape of smaller infarcts in relation to the direction of the fibers of the descending motor tracts are likely to have important effects on functional outcome. Infarcts are commonly ellipsoid rather than spherical. If the number of damaged descending fibers determines functional impairment, then small lesions with their long axis oriented parallel to the descending tracts that have a relatively small cross-sectional area of intersection would not be expected to produce as great a deficit as lesions of similar volume and shape with their long axis oriented perpendicular to the descending fibers. The location of small infarcts with respect to the density of fiber tracts is also likely to be important, and the use of the measurement of the maximum proportion of the cross-sectional area of the mask occupied by stroke incorporates this factor. In a series like this, in which the patients were selected for motor deficit, lesion location is not as important for large infarcts, because the large size of the lesions makes them likely to involve all or most of the cross-sectional area of the corticospinal tract, as shown in Figure 3.

It is important to appreciate that the correlation between Barthel Index and measures of lesion volume were less strong than those for motor deficit and lesion volume. The different relationships between MRI measures and the Barthel Index and between MRI measures and motor deficit illustrate the effect of the use of different outcome measures. The Barthel Index is a measure of the ability to perform various activities of daily living and thus is a measure of disability rather than impairment. Although motor impairment is related to the Barthel Index in that patients with severe levels of impairment are often disabled, it is possible for patients who are well adapted to their deficits to be able to perform all activities of daily living unassisted and hence to score highly on the Barthel Index.

The strong relationship between the maximum proportion of the mask occupied by stroke and NAA loss at the level of the internal capsule indicates that the extent of axonal injury in a specific functional pathway can be measured by the mask.
method. It is interesting that the maximum cross-sectional area of the mask occupied by stroke predicted NAA reduction in the internal capsule better than motor impairment. This is probably a reflection of the combination of error in the measurement of motor impairment and slight variations in recovery between patients with similar degrees of descending motor pathway damage. Quantitative interpretation of MRI with respect to a neuroanatomic mask has intrinsically greater spatial resolution for pathological change than does MRS. In addition, because the mask method requires conventional imaging only, it can be performed without prolonging patient scanning time. Interpretation of studies with newer imaging methods, such as diffusion-weighted or perfusion imaging, may also be improved by quantitative estimates of functional pathway interruption using a probabilistic anatomic mask in a standard brain space as we have described.

There are several limitations to our study. First, only the descending motor fibers from the primary motor area were defined (fibers descending from other motor areas were not included), and this definition was only approximate for any individual owing to the use of a standardized mask, the variation in gyral patterns and brain size between individuals, and individual variation in the course of the corticospinal tract through the corona radiata. It is possible that more accurate results would have been obtained if a mask for each individual patient’s brain had been defined and applied to that individual’s scan in native space. However, the aim of this study was to develop a technique that could eventually be used in a semiautomated fashion on large numbers of patients. This would not be possible if the method required defining masks for each brain separately. A second limitation is that the T2-weighted MRI slices that were used for lesion segmentation were relatively thick at 5 mm. It has been shown in studies of multiple sclerosis that thicker-slice MRI data sets can underestimate lesion volume, particularly when lesions are small. It is also possible that the T2-weighted changes were associated with some degree of pathological heterogeneity. However, because all the patients included in the study were ≥1 month after stroke, most of the edema that occurred as a result of infarction would have been expected to have resolved. The fact that there was a very strong correlation between the maximum proportion of the mask area occupied by stroke and the NAA loss in the internal capsule would suggest that in this study at least, the T2-weighted lesions were reasonably homogeneous in terms of the amount of cell damage.

In conclusion, we have illustrated how the application of a mask of the descending motor pathways to MR images of brain infarction in a common stereotaxic brain space can be used to obtain quantitative functional neuroanatomic data relevant to understanding functional deficits after stroke. The maximum cross-sectional area of the mask occupied by stroke was more highly correlated with motor deficit than the total stroke volume and appeared to be a more sensitive and discriminatory measure for determining motor deficit, particularly for smaller strokes. Future experiments should include a prospective longitudinal study to determine whether use of a corticospinal mask can predict motor outcome in acute stroke. Eventually, it may be possible to apply this approach in an automated way that may assist in the early estimation of the prognosis of stroke patients.

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