Functional Reorganization of Motor Cortex Increases With Greater Axonal Injury From CADASIL

H. Reddy, MD; N. De Stefano, MD; M. Mortilla, MD; A. Federico, MD; P.M. Matthews, FRCP

Background and Purpose—Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited small-artery disease that clinically involves only the brain. Particularly early in the disease, patients can show substantial or complete recovery after individual strokes. Cortical functional reorganization may contribute to limiting disability with such ischemic injury. We sought to test whether the extent of any functional changes in the motor cortex increases with greater brain axonal injury from CADASIL.

Methods—Functional MRI (fMRI) was used to characterize cortical activation during a simple hand-tapping task. Disease-associated pathology in subcortical white matter was assessed with the use of conventional fluid-attenuated inversion recovery (FLAIR) MRI and MR spectroscopic imaging for measurement of N-acetyl aspartate decreases, a relatively specific measure of axonal injury.

Results—There was evidence for variable but substantial hyperintense white matter signal in all of the patients with FLAIR imaging. With the use of fMRI, the brain regions activated during motor tasks were similar for the 9 CADASIL patients and 7 controls, except that most (6 of 9) patients showed primary motor cortex activation both ipsilateral and contralateral to the hand moved, a finding in only 1 of 7 healthy controls. Ipsilateral motor cortex activation increased ($r=−0.77$, $P<0.05$) and motor cortex activation lateralization index decreased ($r=0.68$, $P<0.02$) with greater white matter injury (as assessed from decreases in the relative N-acetyl aspartate concentration) in a region of interest including descending motor fibers of the corticospinal pathway.

Conclusions—The extent of functional reorganization of motor cortex increases with increasing axonal injury, consistent with an adaptive role for these changes. Increased functional recruitment of cortex ipsilateral to the limb moved therefore may contribute to limiting motor impairment from the subcortical injury of CADASIL. (Stroke. 2002;33:502-508.)

Key Words: CADASIL ■ cerebral cortex ■ magnetic resonance imaging ■ motor activity ■ stroke

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited small-artery disease that clinically affects only the brain.1,2 It has been shown to be a consequence of mutations in the notch3 gene on chromosome 19.3 Patients typically present with a suggestive clinical presentation from focal deficits is good, but there is a progressive accumulation of disability later in the disease. The diagnosis currently is established by a suggestive clinical presentation or family history and characteristic pathology in the brain or peripheral vessels,4 demonstration of linkage to chromosome 19 in familial cases,5 or direct definition of a potentially pathological mutation in the notch3 gene.6 Multiple mechanisms could contribute to functional recovery after ischemic injury in CADASIL. For example, functional impairments arising from injury to glial cells may be repaired by their regeneration from precursor cells.8 Resolution of secondary inflammatory changes may remove substances that inhibit or are toxic to axons.9,10 In addition, adaptive reorganization of brain functions could occur, particularly in the early stages of disease.11 Evidence for preservation of a significant degree of cortical “plasticity” even in the adult brain now has been demonstrated for other forms of ischemic disease,12-15 as well as brain injury from mass lesions16 or multiple sclerosis.17-20 Two factors have limited interpretation of previous studies probing potential functional reorganization associated with ischemic injury. The first has been the difficulty of quantifying the extent of injury (as opposed to the consequent functional impairment). This reflects problems both with assessment of the severity of local tissue damage with the use of current imaging techniques and the use of imaging techniques that are insensitive to the severity of local tissue damage. Despite these difficulties, there is abundant evidence that functional reorganization can contribute to recovery after focal ischemic injury.21-27

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of conventional imaging methods and in the localization of lesions with respect to functional pathways. A second and related problem has been the heterogeneity of pathology giving rise to ischemic strokes.

One of the most specific noninvasive measures of brain pathology in vivo is provided by MR spectroscopic imaging (MRSI), which can measure the local concentration of N-acetyl aspartate (NAA), a compound found primarily or solely in mature neurons in the adult brain. Decreases in the brain NAA concentration are a marker of axonal injury or loss. Performed in conjunction with conventional MRI, MRSI allows spatial localization of this measure of axonal injury in specific regions of white matter, which can be defined with respect to functionally relevant white matter tracts on the basis of neuroanatomical landmarks in a coregistered structural MRI scan. NAA decreases in the corticospinal tract have been shown to correlate well with measures of motor functional impairment after stroke and in patients with multiple sclerosis. NAA decreases correlate well with changes in patterns of cortical activation on fMRI in multiple sclerosis, as well as measures of clinical disability. It is important to determine whether cortical functional reorganization is related more generally to the extent of axonal injury.

Patients with CADASIL are particularly suitable for investigation of the relationship between ischemic brain injury, functional reorganization, and disability because they may have a broad range of disability yet share a common underlying etiology and type of pathology. Functional MRI (fMRI) can be used in such an investigation to define abnormal patterns of brain activation arising from disease. Correlation of results with MRSI allows the effects of axonal injury on pattern of cortical activation to be defined quantitatively.

In this study we wished to determine whether reorganization of the motor cortex accompanies axonal damage from the subcortical ischemia of CADASIL and whether the degree of reorganization is related directly to the severity of injury. To do this, we studied 7 normal controls and 9 patients with CADASIL using both MRSI and fMRI with a simple hand-tapping motor task.

### Subjects and Methods

#### Patients

Thirteen patients with CADASIL followed as outpatients at a specialist neurological center were approached for participation in the study, and 9 right-handed patients (aged 25 to 55 years) agreed to participate in the study. Patients were from 5 different families and were diagnosed with either demonstration of a mutation in the notch3 gene or linkage to chromosome 19 haplotype in familial cases. Clinical, neuropathological, and genetic data for 3 of the 5 families were reported previously. The extent of disability was variable among the patients, with Rankin Scale scores ranging from 0 to 5 (Table 1). Clinical deficits were defined initially independently of the MRSI and fMRI studies. Seven (for fMRI) or 11 (for MRSI) healthy right-handed controls (aged 23 to 45 years) also were imaged. The imaging studies were performed in the Neurometabolic Unit of the University of Siena according to protocol approved by the Ethics Committee of the Faculty of Medicine of the University of Siena, and informed consent was obtained from each subject.

#### MR Spectroscopic Imaging

Patients underwent combined brain proton MRI/MRSI examination with a Philips Gyroscan NT system operating at 1.5 T (Philips Medical Systems). On each MRI/MRSI examination, sagittal images were used to identify the anterior commissure and posterior commissure. Multislice fluid-attenuated inversion recovery (FLAIR) images (repetition time [TR]= 9000 ms; echo time [TE]= 150 ms; slice thickness, 4 mm) were obtained in the transverse plane parallel to the anterior commissure–posterior commissure line. These MR images were used to select an intracranial volume of interest for spectroscopy centered on the corpus callosum and measuring approximately 100 mm anteroposterior x 20 mm craniocaudal x 90 mm left to right. This included gray matter and white matter of both hemispheres. Two-dimensional spectroscopic images were obtained with the use of a 90°-180°-180° pulse (PRESS) sequence (TR=2000 ms; TE=272 ms; 250-mm field of view; 32 x 32 phase-encoding steps; 1 signal average per step), as previously described. Magnetic field homogeneity was optimized to a line width of approximately 5 Hz over the volume of interest with the use of the proton signal from water. Water suppression was achieved by placing frequency-
selective excitation pulses at the beginning of the MRSI sequence. Before the water-suppressed acquisition, another MRSI was acquired without water suppression (TR=850 ms; TE=272 ms; 250-mm field of view; 16×16 phase-encoding steps) to allow for B₀ homogeneity correction.

The MRSI data were analyzed in Siena independently of the fMRI data. Postprocessing of the raw MRSI data included zero-filling the non–water-suppressed MRSI to obtain 32×32 profiles, followed by a mild gaussian k-space filter and an inverse 2-dimensional Fourier transformation to both the water-suppressed and unsuppressed MRSI. Artifacts present in the time domain water-suppressed signal as a result of static magnetic field inhomogeneities and time-varying gradients were corrected by dividing the water-suppressed MRSI signal by the unsuppressed signal, a procedure that does not affect relative signal intensities. The residual water signal was then fitted and removed from the water-suppressed data with the use of the Hankel singular-value decomposition procedure. To enhance the resolution of the spectral peaks, a lorentzian-to-gaussian transformation was applied before Fourier transformation in the spectral domain. The nominal voxel size was 8×8×20 mm, giving a resolution of approximately 12×12×20 mm after k-space filtering.

Metabolite resonance intensities of NAA and creatine were determined automatically from peak areas relative to a spline-corrected baseline. Results were expressed as the intravoxel ratio of NAA/creatinine (a signal arising mainly from both creatine and phosphocreatine). Because creatine might change in lesions, an additional measurement of NAA and creatine resonance intensities was made by normalizing metabolites for the water signal collected in the unsuppressed MRSI acquisition. For the purposes of this study, values of metabolite resonance intensities were determined from an average of the values obtained in voxels (n=4 to 6) localized in the left periventricular white matter, including the course of the corticospinal tract predicted from the relative positions of the overlying precentral gyrus and the genu and posterior limb of the internal capsule. Slightly different numbers of voxels were chosen for different individuals for averaging to account for differences in sizes of the ventricles as a result of atrophy.

Functional MRI
fMRI acquisition was done on the same Philips Gyroscan NT system operating at 1.5 T (Philips Medical Systems). Blood oxygen-dependent contrast echo planar imaging scans were performed (TR=3 seconds; 25-cm field of view; 64×64 matrix for 10×7-mm slices). A “block” design was used in which 30 seconds of cued finger tapping was alternated with a 30-second rest period for a total of 5 paired blocks. A total of 100 volumes were obtained, with 10 scans acquired during each block. Tapping involved visually cued (a small flashing red light for cues was positioned just beyond the end of the scanner bed, where it could be viewed with prism glasses) grouped 4-finger flexion-extension movements of the right hand at the metacarpophalangeal joints. The rate of tapping corresponded to 75% of that for each individual’s maximum rate to correct for performance differences. The maximum rate was measured before each scan by asking subjects to tap their fingers as fast as possible for 10 seconds; the maximum rate was taken as the average rate over this period.

fMRI image analysis was performed in Oxford without knowledge of MRSI results with the use of an in-house modified version of MEDx 2.0 (Sensor Systems). Active images were grouped and compared with rest images, and a t test was applied and thresholded at a Z value of 5.1. The final activation map was set for a corrected significance of P<0.01, with the spatial clustering of this thresholded activation taken into account. This statistical image was then registered into high-resolution structural MRI space and overlaid on a structural image. Three regions of interest were defined anatomically, and significantly activated voxels within each were counted. The primary motor cortex included the volume bounded by the interhemispheric fissure medially, the central sulcus posteriorly, the precentral sulcus anteriorly, and the sylvian fissure laterally. The premotor area included those regions in the middle frontal gyrus posterior to the anterior commissure. The supplementary motor area (SMA) was defined in the superior frontal gyrus posterior to the anterior commissure and anterior to a point midway between the precentral sulcus and the anterior limit of the brain. The “motor cortex” includes both the primary motor cortex and the premotor cortex either ipsilateral (IMC) or contralateral (CMC) to the hand moved. The motor activation laterality index (LI) was calculated as (C−I)/(C+I), where C and I are the number of voxels activated in primary motor plus premotor areas contralaterally and ipsilaterally, respectively.

Statistical Analysis
The averaged values of periventricular white matter NAA/creatinine and NAA/water MRSI signal intensity ratios for the group of CADASIL patients were compared with those of the normal controls with the nonparametric Kruskal-Wallis test. Other group differences were tested with Student’s t test. Correlations were tested with a Spearman rank order correlation as implemented in SPSS version 9 (www.spss.com). On the basis of our previous studies of multiple sclerosis patients, the primary hypothesis to be tested was whether the relative ipsilateral motor cortex activation increased with greater brain injury (assessed as a lower white matter NAA/creatinine ratio).

Results
Nine patients with CADASIL were studied (Table 1). One (patient 9) was asymptomatic and had been identified on the basis of family history. The others had variable presentations with symptoms of migraine, partial epilepsy, or stroke. All had substantial regions of abnormal hyperintense FLAIR signal in the white matter, although the character of this abnormality was variable (Figure 1) and the total volume showed no simple relation with disability (data not shown).

We used fMRI to test for functional reorganization in the cortical areas associated with movement. Patients were trained in the motor task before scanning and monitored visually during the fMRI examination by an observer positioned at the end of the magnet bore to ensure compliance with the protocol. The hand at rest and the moving hand were observed carefully. No mirror movements were seen in any of the subjects during the hand tapping. The simple distal hand movements were performed with the proximal arm well supported, and proximal muscle recruitment was not appreciated by the observer during training sessions or while the subjects performed the task in the magnet.

There were similar patterns of brain activation in patients and controls. Both showed task-associated changes in the CMC and the SMA. All subjects also showed significant
activation in the IMC, but for the controls this was predominantly in the posterior middle frontal gyrus (premotor cortex) (6 of 7) rather than the precentral gyrus (primary motor cortex) (1 of 7), while most of the patients showed both ipsilateral primary motor (6 of 9) and premotor cortex (9 of 9) activation. Ipsilateral cerebellar activation also was appreciated consistently in the patients and controls but will not be discussed further because the imaging volume did not include the full cerebellum, precluding a complete description.

The mean overall extent of activation in these regions (measured as the number of voxels showing significant activation above the Z=5.1 threshold) also was similar between the controls and patients (Table 2). There were no significant differences in mean IMC or SMA activation between the 2 groups. There were trends for the mean CMC to be lower (P<0.06) and for the ipsilateral primary motor cortex activation to be greater (P<0.05) in patients relative to controls (Table 2). Ipsilateral primary motor cortex activation contributed 39±32% to the total IMC activation compared with only 4±15% for the controls. However, because the patients have a variable extent of injury, a more powerful approach to defining the relationship between axonal damage and functional imaging changes is to relate individual pathology and fMRI measures.

To provide an index of descending motor fiber injury, MRSI studies were performed to assess axon damage and loss in a white matter region defined to include the corticospinal tract contralateral to the hand moved from the relative NAA/creatine ratio (Table 2). The primary hypothesis to be tested was whether changes in cortical activation patterns are found in proportion to the extent of axonal injury. We found that decreases in the NAA/creatine ratio in the contralateral periventricular white matter were correlated with increasing IMC activation (r=-0.77, P<0.05) (Figure 2) and with a decreasing motor cortex activation LI (r=0.68, P<0.02) (Figure 3).

To ensure that the decreases in NAA/creatine reflect decreases in NAA concentration rather than increases in creatine concentration, both NAA and creatine resonance intensities were measured with respect to the local brain water signal, a quantification method that provides a more direct index of concentrations of the individual metabolites. As confirmation that decreases in NAA/creatine for patients are primarily a measure of the relative change in NAA, the water-normalized NAA intensity was 18% lower in the patients (31.2±7.0 U) relative to the controls (37.9±5.0 U; P=0.04), while the creatine intensity was not significantly

### Table 2. Extent of Activation, LI, and Relative Metabolite Ratios*

<table>
<thead>
<tr>
<th>Patients and Controls</th>
<th>CMC, No. of Voxels</th>
<th>IMC, No. of Voxels</th>
<th>SMA, No. of Voxels</th>
<th>LI</th>
<th>NAA/Cr</th>
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<td><strong>59±20</strong></td>
<td><strong>156±91</strong></td>
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*Extent of activation is measured by number of voxels initially thresholded at Z=5.1 with cluster probability at P<0.01. In functionally defining cortical activation regions, the precentral gyrus was identified as the primary motor cortex, and activation in the posterior middle frontal gyrus was identified as premotor cortex.

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**Figure 2.** Correlation between an index of white matter axonal injury or loss (NAA/creatine ratio) and the number of pixels exceeding threshold in the ipsilateral motor cortex (IMC activation) for the patients (r=−0.77, P<0.05).

**Figure 3.** Correlation between an index of white matter axonal injury or loss (NAA/creatine ratio) and the motor cortex LI (r=0.68, P<0.02).
different between the 2 groups (patients, 10.2±2.0 U; controls, 11.5±1.8 U; \( P=0.15 \)).

**Discussion**

We have shown that quantitative changes in motor cortex activation occur with subcortical injury from ischemic disease in patients with CADASIL. Previous work has shown that patients with focal ischemic injury show relatively greater activation of the ipsilateral motor cortex with hand movement.12-14,32-35 Our study emphasizes that even diffuse subcortical damage of the type seen here is associated with a greater ipsilateral cortical activation with hand movement, as demonstrated in recent studies of cortical reorganization with multiple sclerosis.17-19 A more bihemispheric pattern of motor cortex activation that is therefore likely is a general consequence of axonal injury, regardless of cause. Thus, in addition to the local reorganization of the cortex emphasized in animal studies36 and also demonstrated in some human lesion studies16,19,37 longer-distance functional changes in the motor network appear to be a general part of the injury response of the brain.

However, what is perhaps most significant about the present results is that, with a group of patients showing homogeneous etiology for strokes, there is a direct relationship between the severity of injury and the extent of such homogeneous etiology for strokes, there is a direct relation-

The observations that increased IMC activation can be found in multiple sclerosis patients who show evidence of significant axonal injury but who are without clinically apparent motor deficits18 and that an abnormally low LI after stroke can be found in patients with good functional recovery of movements12,13 have been interpreted as evidence that recruitment of the IMC is part of an adaptive response contributing to recovery. These observations also argue that the finding is not a nonspecific consequence of altered task performance. An alternative hypothesis is that the lower LI is simply a marker of brain injury affecting the motor tract. This was argued earlier by Netz et al,41 who studied a group of patients with heterogeneous lesion load and reported that increased ipsilateral transcranial magnetic stimulation responses were correlated with poorer recovery after stroke. A recent longitudinal fMRI study of patients after stroke showing increasing LI with the progression of recovery could be interpreted as consistent with this notion.32 Direct evidence for the functional significance of IMC activation is limited, but transcranial magnetic stimulation studies have shown enhanced responses to ipsilateral motor stimulation after stroke.42 Combining magnetic stimulation transient interference studies43 and fMRI offers an attractive strategy for defining these phenomena further.

Previously it was noted that there is variability in the extent of activation in the CMC in stroke patients relative to controls.14 The observations here may benefit from the subcortical focus and relative homogeneity of the type of pathology. We found a modest trend toward decreased CMC activation with greater subcortical axonal injury. By inference, this finding is consistent with the notion that greater CMC activation is correlated with better function.12,32 However, alterations in activation throughout the motor network likely also have roles, so that (as suggested in a longitudinal study17) there may not be a simple monotonic relationship between disability or functional impairment and the extent of activation.

A potential confounding factor to interpretation of the present study arises from differences in rates of hand-tapping performance by the subjects. However, if performed at a constant rate by all subjects, the hand-tapping task would have been significantly more difficult for the patients than the...
controls. Since activation increases with task difficulty (apparent complexity or rate), such a design would have biased our results in favor of detecting a difference (increased activation particularly in the IMC) between the patient and control groups and reduced the specificity with which the result could be interpreted.

A technical concern in interpreting any changes in fMRI activation in stroke or multiple sclerosis patients is that local perfusion changes (eg, because of the underlying cerebrovascular disease) or altered neuronal-hemodynamic coupling (eg, with the release of inflammatory factors) could alter the relationship between the blood oxygen–dependent contrast response and the underlying neuronal events. However, the maximum magnitude of the activations in common areas (eg, CMC) was similar for patients and controls (data not shown), and in CADASIL the pathology is predominantly subcortical. The dissociation of changes in IMC (greater extent in patients and CMC (trend to a lesser extent in patients) makes it less likely that either global perfusion deficits or inflammatory changes in blood vessels are dominating the responses seen. Another potential concern is that differences in extent of activation could be driven in part by differences in brain size. While subcortical ischemic disease can be associated with atrophy (and modest changes are apparent in the MRI in Figure 1, for example), which potentially could contribute somewhat to the trend for a decrease in CMC activation, this would not be expected to contribute to the increases in IMC activation that form the basis for our primary conclusions.

The MRSI measure of NAA/creatine, which was the primary index of change, is a relative measure of NAA decrease. While a recent cell culture study was interpreted as the primary index of change, is a relative measure of NAA decrease. While a recent cell culture study was interpreted as offering evidence that under some conditions oligodendroglial cells may express NAA, immunohistochemical localization in the adult rat brain shows that only neurons and their processes have significant amounts of NAA. The NAA/creatine ratio is a relatively sensitive index because it does not rely on comparison with an external standard. Pathological processes (eg, multiple sclerosis) leading to axon injury and loss with secondary gliosis show little or no change in the creatine resonance intensity, suggesting that any decrease in the NAA/creatine ratio is primarily a measure of loss in NAA. Thus, we have confidence in performing our primary analysis relating axonal injury and functional changes to the NAA/creatine ratio. This notion was supported by evidence that the brain creatine/water ratio was unchanged in the patient group.

The relevance of either an absolute or relative NAA concentration measure to understanding pathological factors related to progression of functional impairment is therefore further emphasized by our results. Less specific measures of injury (such as the hyperintense changes on FLAIR imaging reported here) may not show a strong relationship to either functional activation or (in other contexts) disability changes.

In summary, the results of this study confirm that there are altered cortical motor activation patterns after the diffuse subcortical strokes from CADASIL. These changes are consistent with an adaptive cortical response to the ischemic damage, suggesting that enhancement of such changes might promote recovery. An uncertainty with previous similar observations has been to distinguish reorganization that is simply a response to injury (an injury “marker”) and reorganization that is functionally adaptive. Here we provide novel data from a stroke population with a homogeneous underlying pathology showing that the functional changes in motor cortex activation are related directly to measures of the severity of the subcortical pathology, in support of the interpretation that the changes are functionally adaptive. Future work integrating fMRI and electrophysiological studies (eg, functional interference studies using transcranial magnetic stimulation) could provide further evidence since it may be predicted that, if the reorganization is adaptive, patients should show functional interference effects with stimulation of the IMC that parallel the decrease in LI.

Acknowledgments

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References


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