In chronic neurological disorders, both brain and cognitive reserves modulate the clinical impact of chronic brain diseases. Whether a motor reserve also modulates the relationships between stroke and disability is unknown. We aimed to determine whether the shape of the central sulcus, a marker of the development of underlying motor connections, is independently associated with disability in patients with a positive history of small subcortical ischemic stroke.

Methods—Shapes of central sulci were reconstructed from high-resolution magnetic resonance imaging and ordered without supervision according to a validated algorithm in 166 patients with a positive history of small subcortical ischemic stroke caused by CADASIL (Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy), a severe monogenic cerebral small vessel disease affecting young patients. Ordinal logistic regression modeling was used to test the relationships between modified Rankin scale, a disability scale strongly weighted toward motor disability, and sulcal shape.

Results—Modified Rankin scale was strongly associated with sulcal shape, independent of age, sex, and level of education (proportional odds ratio =1.19, 95% confidence interval =1.06–1.35; P=0.002). Results remained significant after further adjustment for brain atrophy, volume of lacunes, and volume of white matter hyperintensities of presumed vascular origin.

Conclusions—The severity of disability in patients with a positive history of small subcortical ischemic stroke caused by a severe cerebral small vessel disease is related to the shape of the central sulcus, independently of the main determinants of disability. These results support the concept of a motor reserve that could modulate the clinical severity in patients with a positive history of small subcortical ischemic stroke. (Stroke. 2016;47:1023-1029. DOI: 10.1161/STROKEAHA.115.012562.)

Key Words: CADASIL central sulcus cerebral cortex motor reserve stroke
of stroke and the development of highly variable levels of disability in young patients. The study of a monogenic disorder responsible for small subcortical ischemic strokes in young patients allows reducing the confounding effect of age and of potentially associated prodromal neurodegenerative disorders in the elderly. Additionally, the cerebral cortex is macroscopically largely spared in this disorder, allowing fine analyzes of its morphology.

Methods

Patients

One hundred and ninety patients (123 from Paris and 67 from Munich) with CADASIL (proven genetically) were included in the present study between 2003 and 2009 and were evaluated every 18 months. At each visit, both clinical, biological, and MRI evaluations were performed using harmonized protocols. The present analyses are based on the initial assessment of MRI and clinical data. All patients had a positive history of small subcortical ischemic stroke caused by CADASIL and were aged >18 years. Small subcortical ischemic strokes were defined as neurological deficits lasting more than 24 h linked to a recent small subcortical infarct identified on imaging (computed tomographic scan or MRI). They participated in a prospective cohort study of CADASIL at Lariboisière (Paris) or Ludwig-Maximilians-Universität (Munich). Details of the protocol have been previously reported. Age, sex, and level of education were collected among a large set of clinical and epidemiological data. Disability was assessed using the modified Rankin scale (mRS), a widely used scale heavily weighted toward motor disability, ranging from 0 (no symptom) to 5 (bedridden). An ethics committee approved the study in both centers.

MRI Acquisition

MRI scans were obtained on 1.5-T systems (Siemens Magnetom Vision [Munich] or General Electric Medical Systems Signa [Paris and Munich]). 3DT1 sequences (Munich: repetition time/echo time (TR/TE) = 11.4/4.4 ms, slice thickness = 1.2 mm, no interslice gap, in-plane resolution = 0.9x0.9 mm; Paris: TR/TE = 9.1/2 ms, slice thickness = 0.8 mm, no gap, in-plane resolution = 1.02x1.02 mm), fluid-attenuated inversion recovery (Munich: repetition time/echo time/inversion time (TR/TE/TI) = 4555/110/28 ms, slice thickness = 5.5 mm, no gap, in-plane resolution = 0.8x0.8x0.94 mm), and T2*-weighted gradient echo imaging (Munich: TR/TE = 1056/22 ms, slice thickness = 5.5 mm, no gap, in-plane resolution = 0.98x0.98x0.98 mm; Paris: TR/TE/TI = 8402/161/2002 ms, slice thickness = 5.5 mm, no gap, in-plane resolution = 0.94x0.94x0.94 mm), and T2*-weighted gradient echo imaging (Munich: TR/TE = 4284/110/1428 ms, slice thickness = 0.94x0.94x0.94 mm; Paris: TR/TE/TI = 8402/161/2002 ms, slice thickness = 5.5 mm, no gap, in-plane resolution = 0.94x0.94x0.94 mm, and T2*-weighted gradient echo imaging (Munich: TR/TE = 1056/22 ms, slice thickness = 5.5 mm, no gap, in-plane resolution = 0.98x0.98x0.98 mm; Paris: TR/TE/TI = 8402/161/2002 ms, slice thickness = 5.5 mm, no gap, in-plane resolution = 0.98x0.98x0.98 mm) were performed.

Image Processing

White matter hyperintensities and lacunes of presumed vascular origin as well as microbleeds were extracted using validated methods detailed elsewhere from high-resolution fluid-attenuated inversion recovery, 3DT1, and T2* MRI sequences, respectively, in agreement with the STRIVE (Standards for Reporting Vascular Changes on Neuroimaging) criteria. Volume of white matter hyperintensities, volume of lacunes, and number of microbleeds were measured as previously reported. In a second step, those variables were measured specifically within pyramidal tracts after registration within the Johns Hopkins University probabilistic atlas of major white matter tracts in the Montreal Neurological Institute template. The skewed distributions of the volumes of white matter hyperintensities both globally, within and without pyramidal tracts, these variables were log-transformed to obtain close to normal distributions. Brain parenchymal fraction, a recognized measure of brain atrophy, was defined as the ratio of brain tissue volume to the intracranial cavity volume to take into account differences in head size between patients, as previously detailed.

Reconstruction and identification of cortical sulci were performed using Brainvisa (http://brainvisa.info). Ordering of shapes of central sulci was performed using previously validated methodology. Right central sulci were first flipped relative to the interhemispheric plane to allow comparison with left central sulci (Figure 1). Hence, all analyses included both left and right sulci of each patient. A pairwise shape similarity matrix was computed across the whole set of sulci. The similarity between 2 sulci was coded by the average quadratic distance between their 3-dimensional representations after alignment. This pairwise registration was achieved using the iterative closest point algorithm, which aligns one sulcus relative to the other through successive rotations and translations. The shape similarity matrix was built from all the pairwise comparisons, and manifold learning (using the Isomap algorithm) was used to capture a 1-dimensional approximation of the high dimensional space spanned by central sulci. This 1-dimensional approximation provided a numeric index of sulcal shape (I) for each sulcus relative to all the others (hence each subject had an index for his right central sulcus I_R and one for his left central sulcus I_L). For analyses, an index I_M was calculated for each patient as the average of this numeric index on both sides (Figure 1).

Statistical Analyses

Statistical analyses were performed using the R software (http://www.r-project.org/). To determine whether mRS is independently related to I_M, we used ordinal logistic regression analyses to determine the regression coefficients on the log scale that were further exponentiated to obtain proportional odds ratios (OR) together with their 95% confidence interval (95% CI). In model 1, univariate analysis was tested, with mRS as the dependent variable and I_M as the independent variable. In model 2, I_M, age, sex, and level of education were included as covariates. In model 3, I_M, age, sex, level of education, brain parenchymal fraction, volume of lacunes, volume of white matter hyperintensities, and number of microbleeds were included as covariates, those imaging variables being associated with disability in cerebral small vessel disease in general and in CADASIL in particular. In model 4 (full model), the same covariates as model 3 were included, but volume of lacunes, volume of white matter hyperintensities, and number of microbleeds were evaluated separately within and outside pyramidal tracts and considered as different covariates. The different models were compared by analysis of variance.

Results

Among 190 CADASIL patients with a positive history of small subcortical ischemic stroke caused by CADASIL who were recruited in the 2 centers, 6 were excluded from analyses because they also had a large cortical infarct on MRI. Seven had incomplete MRI data or MRI data of insufficient quality for image processing. For 11 patients, the reconstruction of one or the other central sulcus failed for various technical reasons, leaving 166 patients for analyses. Characteristics of those 166 patients are given in Table 1. Fifty-three percent of patients experienced ≥2 small subcortical ischemic strokes, whereas 28% had ≥3.

We observed that the first source of variability regarding the shape of central sulci among CADASIL patients was the vertical position of the hand knob along the central sulcus together with a decrease of its size when shifted upward (Figure 1). A scatterplot of the rough relationships between sulcal shape (I_M) and mRS is presented Figure 2.

In univariate ordinal logistic regression analysis, mRS was significantly associated with I_M (OR = 1.20; 95% CI = 1.07–1.35; P = 0.002). In other words, for a 1-unit increase in I_M, the odds to move from a low or intermediate mRS to a larger mRS were increased by 20%.
increase by 20% (multiplied by a factor of 1.2), with upper and smaller hand knobs being associated with larger mRS.

In model 2, including age, sex, and level of education as covariates, mRS was significantly associated with $I_{RL}$ (OR$_P$=1.19, 95% CI =1.06–1.35; $P$=0.004), age (OR$_P$=1.08, 95% CI =1.04–1.12; $P<10^{-4}$), and level of education (OR$_P$=0.69, 95% CI =0.52–0.90; $P$=0.006), but not sex (Table 2). Model 2 performed statistically significantly better than model 1 ($P<10^{-4}$).

In model 3, further including as covariates brain parenchymal fraction, volume of lacunes, volume of white matter hyperintensities, and number of microbleeds, mRS was significantly related to $I_{RL}$ (OR$_P$=1.19, 95% CI =1.05–1.35; $P=0.005$), brain parenchymal fraction (OR$_P$=0.88, 95% CI =0.81–0.96; $P<10^{-4}$), and level of education (OR$_P$=0.73, 95% CI =0.55–0.97; $P=0.03$), but not to age, sex, volume of lacunes, or of white matter hyperintensities or number of microbleeds. Model 3 performed statistically significantly better than model 2 ($P=0.0009$).

In the full model (model 4) including volume of lacunes, volume of white matter hyperintensities, and number of microbleeds evaluated separately outside and within pyramidal tracts, mRS was significantly associated with $I_{RL}$ (OR$_P$=1.23, 95% CI =1.09–1.41; $P=0.002$), the volume of lacunes measured within pyramidal tracts (OR$_P$=1.01, 95% CI =1.00–1.01; $P=0.01$), the number of microbleeds measured outside pyramidal tracts (OR$_P$=1.11, 95% CI =1.02–1.22; $P=0.009$), brain parenchymal fraction (OR$_P$=0.86, 95% CI =0.79–0.94; $P<10^{-4}$), and level of education (OR$_P$=0.74, 95% CI =0.55–0.98; $P=0.03$). The full model performed statistically significantly better than model 3 ($P=0.003$). The inclusion of center as a fixed effect in the 4 different models did not alter the results.

**Discussion**

The results of the present study show that, in a large cohort of young patients all affected by the same severe monogenic cerebral small vessel disease responsible for small subcortical ischemic strokes, the severity of disability is independently associated with the shape of the central sulcus, mostly driven by the vertical position and the size of the hand knob, as reported previously in healthy subjects. An index was determined for each central sulcus respective to the whole sample of central sulci. The $I_{RL}$ index for a subject was obtained by averaging right and left indexes.
(mostly related to available tissue resources and components) that can modulate the clinical expression of brain pathologies both in young and older populations. Whether our findings are specific to CADASIL or can be generalized to other types of cerebral small vessel diseases or to other stroke populations will of course require further investigations. In particular, although all the patients included in the present study experienced at least one small subcortical ischemic stroke, 53% of them experienced ≥2 small subcortical ischemic strokes. Moreover, in these patients, the whole burden of lacunes, a large proportion of which did not lead to stroke, is a major determinant of disability compared with other etiologies of stroke. Others and we have previously shown that the cortical mantle can be altered secondary to subcortical lesions in cerebral small vessel diseases. In the present study, we cannot formally exclude that the observed cortex shape variations between patients are in fact the remote cortical consequences of subcortical strokes and lacunes on connected fiber bundles. However, it is important to note that the pattern of variations of shapes of central sulci detected by our unsupervised algorithm was very similar to that of healthy individuals. This strongly argues against the hypothesis that the variations observed in patients results from remote effects of subcortical lesions, but rather support the hypothesis that they actually represent a developmental marker independent of the effects of the disease. In addition, by contrast to other MRI measures, the shape of the central sulcus seems highly stable during lifespan, also rendering less likely the possibility of secondary alterations. In our cohort, >30 patients are being followed using MRI acquisitions every 18 months since >12 years, and the shape of the central sulcus is largely unaltered as illustrated by a typical case even when they develop disability (Figure 3).

After stroke, motor recovery seems highly variable among individuals. Both structural and functional reorganization occur not only locally but also remotely to the stroke lesion. Bilateral modulations of sensorimotor activations have been consistently observed and may predict motor recovery after stroke. The integrity of pyramidal tracts measured using various quantitative measures of diffusion and electrophysiological

| Table 1. Clinical and MRI Data of the 166 Patients |
|----------------------------------|------------------|
| **Clinical Data**                |                  |
| Age, mean±SD (range)            | 52.2±9.7 (31.4–77.5) |
| Male sex, count (%)             | 84/166 (51%)     |
| Level of education, count (%)   | Basic: 24 (14%)  |
|                                 | Secondary: 109 (66%) |
|                                 | University: 27 (16%) |
| Number of subcortical ischemic strokes, count (%) | 1: 79 (47%) |
|                                  | 2: 41 (25%)      |
|                                  | ≥3: 46 (28%)     |
| Modified Rankin scale, median, interquartile range, range | 1, 2, 0–5 |
| Time elapsed in days between first stroke and current study, median, interquartile range, range | 1203, 1675, 17–6655 |
| Time elapsed in days between last stroke and current study, median, interquartile range, range | 471, 993, 17–6258 |
| **Imaging data**                |                  |
| Brain parenchymal fraction, %, mean±SD (range) | 84.2±6.1 (65.3–96.1) |
| Volume of lacunes, mm³, mean±SD (range) | 478±671 (0–3864) |
| Volume of white matter hyperintensities of presumed vascular origin, mm³, mean±SD (range) | 113140±68273 (3796–414400) |
| Number of microbleeds, mean±SD (range) | 3.7±12.7 (0–123) |

MRI indicates magnetic resonance imaging.

Figure 2. Relationships between sulcal shape and modified Rankin scale. Scatter plot representing the rough relationships between the index of sulcal shape and modified Rankin scale. The line of best fit obtained with ordinary least square regression is shown with its 95% confidence interval. The suggested link was confirmed by ordinal regression analyses (see the results section). Please note that a small amount of random noise was added on the horizontal axis to allow a better visualization, particularly regarding scores 0 and 1 of modified Rankin scale for which several points would have been otherwise overlaid onto each other.
parameters was found promising to help predict motor recovery,24,25 although the yield of these techniques compared with clinical data alone remains undetermined.26 Analysis of sulcal morphology is independent from all these methods and may provide additional information to better determine the patients who will more likely benefit of neurorehabilitation.26 Whether sulcal shape can help in predicting long-term disability in patients having initially the same level of motor impairment will require further investigations.

Our study has several limitations. We studied patients with CADASIL, a rare monogenic disorder, thus questioning the generalizability of our results to other stroke populations. Also, we used mRS to assess disability while it is not a direct measure of motor function but a general measure of disability. Although in the present cohort we did not plan to measure scores of motor function, pyramidal involvement was tested at each visit. We tested, using a logistic regression model, whether pyramidal involvement was

<table>
<thead>
<tr>
<th>Proportional Odds Ratios</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>( f_{\text{RL}} )</td>
<td>1.20 [1.07–1.35]*</td>
<td>1.19 [1.06–1.35]*</td>
<td>1.19 [1.05–1.35]*</td>
<td>1.23 [1.09–1.41]*</td>
</tr>
<tr>
<td>Age</td>
<td>1.08 [1.04–1.12]†</td>
<td>1.02 [0.97–1.07]</td>
<td>1.04 [0.99–1.09]</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>0.65 [0.34–1.32]</td>
<td>1.17 [0.54–2.54]</td>
<td>1.46 [0.64–3.37]</td>
<td></td>
</tr>
<tr>
<td>Level of education</td>
<td>0.69 [0.52–0.90]*</td>
<td>0.73 [0.55–0.97]‡</td>
<td>0.74 [0.55–0.98]‡</td>
<td></td>
</tr>
<tr>
<td>BPF</td>
<td>0.88 [0.81–0.96]†</td>
<td>0.86 [0.79–0.94]‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume of lacunes§</td>
<td>1.00 [0.99–1.00]</td>
<td>1.00 [1.00–1.00]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume of WHM§</td>
<td>1.77 [0.98–3.41]</td>
<td>2.58 [0.87–8.09]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of MB§</td>
<td>1.01 [0.96–1.07]</td>
<td>1.11 [1.02–1.22]*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume of lacunes in PT</td>
<td>1.01 [1.00–1.01]*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume of WMH in PT</td>
<td>0.60 [0.26–1.45]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of MB in PT</td>
<td>1.01 [0.91–1.11]</td>
<td></td>
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</tr>
</tbody>
</table>

Proportional odds ratios are provided with 95% confidence intervals. BPF indicates brain parenchymal fraction; \( f_{\text{RL}} \), index of sulcal shape; MB, microbleeds; PT, pyramidal tracts; and WMH, white matter hyperintensities.

*Level of significance: <0.01.
†Level of significance: <0.001.
‡Level of significance: <0.05.
§Measured outside pyramidal tracts in model 4.

Figure 3. Stability of sulcal shape over long periods of time. Example of a 46-year-old female CADASIL (Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy) patient, representative of our sample. After a 12-year-long follow-up period, significant whole brain atrophy has developed, with major enlargement of ventricles (lateral, 3rd, 4th), whereas cortical sulci are wider and less deep. By contrast, the global shape of the central sulcus appears stable both on magnetic resonance imaging (MRI) axial slices and on 3-dimensional reconstruction when overlaid on surfaces meshes (please note that MRI slices are conventionally flipped, but meshes are represented through a top-down view, with right hemisphere on right side). Meanwhile, significant disability has developed (mRS score from 0 to 2).
associated with \( I_{mS} \). Results were significant both in univariate analyses and after adjustment for potential confounders. Furthermore, adding pyramidal involvement as a covariate in the different regression models led to lower and less significant effect of \( I_{mS} \) as a predictor of mRS (data not shown). Altogether, these additional results strongly support that the link between \( I_{mS} \) and mRS is actually mostly mediated by motor involvement. Moreover, given the few values allowed by this score (0–5), sampling variations may promote the detection of significant results because of chance alone. However, we found similar results with the Barthel Index, another measure of disability largely independent from the mRS, thus rendering this hypothesis unlikely. We studied sulcal shape on both sides rather than through separated analyses, which is questionable. However, this allowed limiting the number of statistical tests, thus reducing the probability to find significant results because of chance alone. Moreover, given that most patients experienced several small subcortical strokes, separate analyses on both sides would have been very difficult to perform and interpret. Additionally, we could not adjust our results for the initial stroke severity because National Institutes of Health Stroke Scale (NIHSS) at time of previous strokes was not available for most patients. However, our results were left unchanged when taking into account NIHSS at baseline in the present study. As NIHSS at baseline may not match NIHSS at time of stroke, we also checked that the presence of motor symptoms at time of stroke, more likely to be associated with larger NIHSS scores, did not alter our results. Further adjustment for time elapsed since last stroke did not either alter our results. Also, we did not perform diffusion tensor analyses because the strong loss of anisotropy in our cohort would have led to highly unreliable estimates. Finally, although we have adjusted analyses for most known factors associated with the severity of disability in CADASIL, we cannot formally exclude that unidentified confounders could be responsible for our results.

Our study also has important strengths. We have tested our hypothesis in a homogeneous sample of patients who are affected by the same monogenic disorder that is characterized by a normal brain development followed by the occurrence of stroke at a young age. In CADASIL, patients develop various degrees of disability at the same age, despite similar loads of ischemic lesions in the brain, for reasons that are not at all well understood and while brain comorbidities are unlikely. Furthermore, our analyses were unsupervised, and the statistical strategy was straightforward, hierarchical with clear a priori selection of covariates, and with limitation of the number of tests.

In summary, the results of the present study suggest that a simple parameter visible at the surface of the cerebral cortex might be a marker of a cerebral motor reserve modulating the relationships between subcortical ischemic stroke and disability. Further studies are needed to determine whether these results can be generalized to other stroke populations.

Acknowledgments

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Disclosures

None.

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Shape of the Central Sulcus and Disability After Subcortical Stroke: A Motor Reserve Hypothesis

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