Cortical changes in cerebral small vessel diseases: a 3D MRI study of cortical morphology in CADASIL

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Brain atrophy represents a key marker of disease progression in cerebrovascular disorders. The 3D changes of cortex morphology occurring during the course of small vessel diseases of the brain (SVDB) remain poorly understood. The objective of this study was to assess the changes affecting depth and surface area of cortical sulci and their clinical and radiological correlates in a cohort of patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a genetic SVDB. Data were obtained from a series of 69 CADASIL patients. Validated methods were used to determine depth and surface area of four cortical sulci. The ratio of brain to intracranial cavity volumes (brain parenchymal fraction—BPF), volume of lacunar lesions (LL) and of white matter hyperintensities, number of cerebral microhaemorrhages, and mean apparent diffusion coefficient were also measured. Association between depth and surface area of the cortical sulci and BPF, clinical status and subcortical MRI lesions were tested. Depth and surface area of cortical sulci obtained in 54 patients were strongly correlated with both cognitive score and disability scales. Depth was related to the extent of subcortical lesions, surface area was related only to age. In additional analyses, the depth of the cingular sulcus was independently associated with the volume of LL (P = 0.001), and that of the superior frontal sulcus with the mean apparent diffusion coefficient (P = 0.003). In CADASIL, important morphological changes of cortical sulci occur in association with clinical worsening, extension of subcortical tissue damage and progression of global cerebral atrophy. These results suggest that the examination of cortical morphology may be of high clinical relevance in SVDB.

Keywords: brain atrophy; cortical sulci; small vessel disease; MRI; CADASIL

Abbreviations: ADC = apparent diffusion coefficient; BPF = brain parenchymal fraction; CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; DBP = diastolic blood pressure; ICV = intracranial cavity volume; LL = lacunar lesions; MDRS = Mattis Dementia Rating Scale; mRS = modified Rankin’s scale; SBP = systolic blood pressure; WMH = white matter hyperintensities


Introduction

Recent data suggest that cerebral atrophy is a key marker of clinical severity and progression in cerebral small vessel diseases of the brain (SVDB). Both in sporadic and hereditary SVDB, global cerebral atrophy has been found to be strongly related to cognitive decline and disability as well as to the amount of subcortical tissue insults of vascular origin (Preul et al., 2005; Schmidt et al., 2005; Peters et al., 2006). The exact mechanisms underlying this process remain poorly understood. Particularly, some data suggest that cortical atrophy also occurs, although tissue lesions largely predominate in the white-matter and basal ganglia. Wen et al. (2006) recently reported both regional and diffuse loss of cortical grey matter, in line with a
reduction of the cortical ribbon thickness observed by Preul et al., in association with ischaemic white-matter lesions (Preul et al., 2005). However, the loss of contrast between gray and white matter observed with ageing makes these results difficult to interpret (Kochunov et al., 2005).

Recent developments in imaging post-processing techniques now allow us to investigate the 3D morphology of the cerebral surface area. Thus, new features of cortical morphology such as sulcal depth and surface area can be obtained, in vivo, using high-resolution 3D T1-weighted images (Magnotta et al., 1999; Kochunov et al., 2005; Rettmann et al., 2006). We hypothesized that these new tools may be useful to better understand the development and pathophysiology of the atrophy process in SVDB (Kochunov et al., 2008).

In the present study, we used these new tools to assess the 3D morphological aspect of cortical sulci in Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), a monogenic SVDB responsible for a large spectrum of subcortical cerebral lesions typically observed in ischaemic SVDB (Chabriat et al., 1995; Joutel et al., 1996). We analysed the relationships between the morphological aspect of cortical sulci and the following parameters: (i) age and scores of cognitive impairment and disability, (ii) extent of subcortical tissue lesions, (iii) global morphology parameters such as the whole brain volume and volume of ventricles.

**Methods**

**Subjects**

All patients were recruited at Lariboisière Hospital (Paris) between October 2003 and July 2005 among consecutive CADASIL patients aged over 18 years with a positive Notch 3 genetic test. Clinical and demographic data were collected including age, sex, history of hypertension [defined as previous diagnosis of hypertension (≥140/90) or taking anti-hypertensive drugs], systolic blood pressure (SBP), diastolic blood pressure (DBP), diabetes (1997 WHO criteria), history of hypercholesterolemia (previous diagnosis of hypercholesterolemia or taking lipid-lowering drugs), smoking habits, alcohol intake and body mass index. All subjects underwent detailed baseline neurological examination during the 2h preceding MRI examination, including a global evaluation of cognitive performances with the Mattis dementia rating scale (MDRS) and of disability based on the modified Rankin’s scale (mRS). MDRS scores range from 0 to 144 (normal), while the mRS scales range from 0 (normal) to 5 (severely disabled) (Beloosesky et al., 1995; Paul et al., 2001). Manual evaluation including complete blood cell count, glucose, haemoglobin A1c (HbA1c), homocysteine, high-density lipoprotein, low-density lipoprotein and total cholesterol levels was performed in all patients. An independent ethics committee approved this study.

**MRI**

MRI scans were obtained by the use of a 1.5-T system (Signa General Electric Medical Systems). Three-dimensional T1-weighted axial sequences (TR/TE 9/2 ms slice thickness 0.8 mm, no interslice gap, 256 × 256), fluid-attenuated inversion recovery (FLAIR, TR/TE/TI 8402/161/2002 ms, slice thickness 5.5 mm, no interslice gap, 256 × 192), proton density (PD, TR/TE 3300/15 ms, slice thickness 5.5 mm, no interslice gap, 256 × 192) and DWI (TR/TE 8200/83 ms, slice thickness 5.5 mm, no interslice gap, 128 × 128; b value = 1000 s/mm²) were performed. DWI scans were acquired in the X, Y and Z directions and then averaged to make apparent diffusion coefficient (ADC) measurements largely independent of the effects of anisotropic diffusion. ADC values were then calculated to generate ADC maps as described previously (Viswanathan et al., 2006b; Joutel et al., 2007).

**Image processing and analysis**

**Determination of brain volume, ventricular volume and mean-ADC**

Determination of global brain volumes from 3D T1 sequences was performed using Brainvisa software (CEA, Orsay, France, http://brainvisa.info). Details and validation of the segmentation methods have been previously described (Jouvent et al., 2007). This procedure is not affected by the reduction of contrast between gray and white matter occurring with ageing, as it mainly relies on the delineation of boundaries between grey matter and CSF (Mangin et al., 2004). The brain parenchymal fraction (BPF) was defined as the ratio of brain tissue volume to the total intracranial cavity volume (ICV): BPF = brain tissue volume/ICV.

The ventricular volume was determined using the binary cerebrospinal fluid (CSF) mask obtained during the segmentation process and included the lateral and third ventricles. For each case, the delineated volume was checked on all T1 sub-millimeter axial slices crossing the ventricles and marginal corrections were performed manually by the same reader (EJ) when needed.

Histograms of ADC values from ADC maps were generated for each patient using a bin width equal to 0.1 × 10⁻⁴ mm² s⁻¹. Voxels containing CSF were excluded in all patients before calculation using a superior threshold value at 27 × 10⁻⁴ mm² s⁻¹ (value chosen after careful visual analysis of masks generated with different threshold values). To correct for cross subject differences in brain volume, each histogram was normalized to the total number of brain tissue voxels. Only the mean-ADC derived from each histogram was used for analysis.

**Lesions quantification**

Lesions quantification was performed as previously described (Viswanathan et al., 2006b). Briefly, white matter hyperintensities (WMH) were analysed on all axial FLAIR slices from the base of the cerebellum to the vertex. Lacunar lesions (LL) were determined on 3D T1 scans. The total volume of WMH and that of LL were normalized to the ICV in each patient [normalized volume = (volume/ICV) × 100]. The number of cerebral microhaemorrhages (CM), defined as rounded foci ≤ 5 mm in diameter hypointense on gradient-echo sequences and distinct from vascular flow voids, leptomeningeal hemosiderosis or non-haemorrhagic subcortical mineralization, was recorded.

**Delineation of cortical sulci, automated recognition and determination of quantitative morphologic parameters**

Delineation and automatic recognition of sulci were performed using Brainvisa. After segmentation of the brain, the medial surface area of cortical folds was obtained using an erosion procedure.
(Mangin et al., 2004). Sulcal structures, defined as medial surfaces from the two opposing gyrus banks that span from the most internal point of sulcal fold to the most external borders of the cortex, were constructed automatically by the software (Mangin et al., 2004). After resampling of FLAIR data, the FLAIR and 3D T1 images were co-registered using a 12-parameter rigid body algorithm. Then, the mean white-matter intensity on T1 was applied to all voxels on T1-weighted images exactly corresponding to hyperintensities on FLAIR images to avoid artificial detection of gray matter or of sulci inside the white matter.

Thereafter, the cortical sulci were automatically labelled by the software as previously detailed (Riviere et al., 2002). In the present study, four sulci were selected on each hemisphere for analysis: the central sulcus, the superior temporal sulcus, the superior frontal sulcus and the cingulate sulcus. These sulci were chosen because: (i) they are present in all individuals, (ii) they are large and easily identified, thus facilitating error detection, (iii) they are located on different cerebral lobes. In each case, identification of the different sulci was checked by careful visual inspection on 3D images and their labelling was corrected manually only when necessary (Fig. 1). Corrections of the identification of sulci branches were needed with a frequency varying from 1% of sulci for the central sulcus to 10% of sulci for the superior frontal sulcus. Both the surface area and depth (defined as the maximum distance between the internal and external edges of the sulcus skeleton produced by the software) were obtained for each sulcus (eight sulci in total, four on each hemisphere). In order to overcome the inter-individual variability, both surface area and depth were normalized to the ICV before statistical analysis.

Finally, out of 69 consecutive patients who had high-quality MRI scans, a complete dataset with perfect reconstruction of the four sulci on each side (after visual inspection of the results in 3D) was obtained in 54 subjects. To assess the validity and reproducibility of the procedure, 10 patients were randomly selected from this population (mean age: 48; range: 35–65 years). The complete algorithm was run twice in these 10 subjects. The intraclass correlation coefficients for depth and surface area were respectively 0.97 and 0.94. Moreover, the algorithm was run on MRI data obtained twice in 5 of these 10 subjects (18 months interval in the follow-up study). The results also showed high correlation coefficients both for the depth and surface area measurements (0.93 and 0.92, respectively).

In the 15 remaining patients, no or few data were obtained with the original procedure. Alternate algorithms with multiple individual adjustments were then tested to increase the number of available sulci.

**Statistical methods**

Only the data from the 54 patients with complete dataset and perfect reconstruction were used in the main statistical analysis.

Linear regressions models were used to assess the relative contribution of clinical, biological and MRI data on the mean depth and surface area of the cortical sulci (mean value for the eight sulci). The following epidemiological data were included: age, gender, systolic and DBP, homocysteine, cholesterol, fasting glucose and HbA1c values, body mass index, diabetes, history of hypertension and history of hypercholesterolemia. Traditional cardiovascular risk factors such as smoking habits and alcohol intake were also included. Finally, both conventional MRI markers and mean-ADC values were used in the statistical models. A log transformation was performed for normalized volume of WMH, LL and ventricles to obtain normal distributions (vWMH, vLL and vV, respectively). For analysis, number values of CM were divided into tertiles (0, 1–3 or ≥4). Additional analyses for each sulcus were made using mixed-effect models including random subject effects to take into account the multiple measures (one for each side) in each subject.

Multiple linear regression models were used to find predictors of mean depth and surface area. Covariates included in multivariate analysis were those potentially associated with mean depth or surface area in univariate analysis (P < 0.25). The final model variables were selected by a stepwise regression analysis with removal threshold set at P > 0.10. Four different models were constructed: model a: mean depth and cognitive scales or disability scores; model b: mean depth and MRI markers; model c: mean surface area and cognitive scales or disability scores; model d: mean surface area and MRI markers.

For analysis of depth and surface area of each individual sulcus, separate models were constructed. Due to the number of models, the corresponding results were considered significant at P-value < 0.005.

**Results**

**Characteristics of patients**

The main clinical characteristics of the 54 patients for whom complete data were obtained with the original procedure are presented in Table 1. The clinical and radiological characteristics of the 15 remaining cases excluded from analysis

![Fig. 1 Three-dimensional reconstruction of the right central sulcus in one patient included in the study. The sulcus shape is superimposed to one axial slice (top), and over cortical meshes on 3D T1-weighted MRI (bottom).](http://brain.oxfordjournals.org/)

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are also detailed in Table 1. These 15 patients were older, more cognitively impaired had a larger volume of WMH and smaller BPF than the others.

Predictors of sulcal depth

Relationship between mean depth of sulci and cognitive scales or disability scores (Table 2, model a)

In univariate analysis, the mean depth of sulci was correlated with the MDRS ($P = 0.007$) and inversely related to the mRS ($P = 0.0004$). The mean depth was also inversely correlated with age, male sex, diastolic and SBP, increased serum cholesterol and use of antiplatelet agents. In multivariate analysis, the mean depth of sulci remained significantly associated with MDRS scores ($\beta = 2.9 \times 10^{-8}$, $SE = 9.2 \times 10^{-9}$, $P = 0.003$) and inversely related to the mRS ($\beta = –5.7 \times 10^{-7}$, $SE = 1.3 \times 10^{-7}$, $P < 0.0001$). The age effect was no longer significant ($P > 0.4$).

Relationship between mean depth of sulci and MRI markers (Table 2, model b)

In multivariate analysis, the mean depth of sulci was inversely related to male sex ($\beta = –1.19 \times 10^{-6}$, $SE = 4.3 \times 10^{-7}$, $P = 0.0089$), vLL ($\beta = –2.29 \times 10^{-7}$, $SE = 1.2 \times 10^{-7}$, $P = 0.022$) and mean-ADC ($\beta = –2.9 \times 10^{-7}$, $SE = 1.3 \times 10^{-7}$, $P = 0.027$). The age effect was not significant ($P = 0.53$).

Relationship between the depth of different sulci and MRI markers

In additional analyses using mixed effect models, after adjustment for potential confounders, the depth of the cingular sulcus was independently associated with vLL ($\beta = –6.4 \times 10^{-7}$, $SE = 1.8 \times 10^{-7}$, $P = 0.001$), and that of the superior frontal sulcus to mean-ADC ($\beta = –5.7 \times 10^{-7}$, $SE = 1.8 \times 10^{-7}$, $P = 0.003$). The depth of central and superior temporal sulcus were independently associated with male sex ($\beta = –1.58 \times 10^{-6}$, $SE = 3.9 \times 10^{-7}$, $P = 0.0001$ and $\beta = –1.33 \times 10^{-6}$, $SE = 4.88 \times 10^{-7}$, $P = 0.002$, respectively). Only the depth of the superior temporal sulcus was found significantly associated with age ($\beta = –8.7 \times 10^{-8}$, $SE = 3.5 \times 10^{-8}$, $P = 0.02$).

Predictors of sulcal surface area

Relationship between mean surface area of sulci and cognitive scales or disability scores (Table 2, model c)

In univariate analysis, the mean surface area of sulci was found related to age as well as to disability and cognitive scores. In multivariate analysis, the mean surface area was inversely related to mRS ($\beta = –1.58 \times 10^{-6}$, $SE = 3.9 \times 10^{-7}$, $P = 0.0001$ and $\beta = –1.33 \times 10^{-6}$, $SE = 4.88 \times 10^{-7}$, $P = 0.002$, respectively). There was also a trend for an association with the MDRS score ($\beta = –3.9 \times 10^{-6}$, $SE = 2.0 \times 10^{-6}$, $P = 0.06$) in association with age ($\beta = –9.7 \times 10^{-6}$, $SE = 3.6 \times 10^{-6}$, $P = 0.0093$).
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Table 2 Results obtained with univariate analysis of clinical, biological and MRI data for the mean depth and mean surface area of sulci

<table>
<thead>
<tr>
<th>Depth (mean value, 8 sulci)</th>
<th>Surface area (mean value, 8 sulci)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Estimate</strong></td>
<td><strong>Standard error</strong></td>
</tr>
<tr>
<td><strong>Clinical variables</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>–4.9, 10^–8</td>
</tr>
<tr>
<td>Male sex</td>
<td>–1.9, 10^-6</td>
</tr>
<tr>
<td>Left handed</td>
<td>1.2, 10^-7</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>–2.2, 10^-7</td>
</tr>
<tr>
<td>DBP</td>
<td>–5.8, 10^-8</td>
</tr>
<tr>
<td>SBP</td>
<td>–3.2, 10^-8</td>
</tr>
<tr>
<td>BMI</td>
<td>1.9, 10^-8</td>
</tr>
<tr>
<td>Current or previous smoking</td>
<td>–1.1, 10^-7</td>
</tr>
<tr>
<td>Any alcohol consumption</td>
<td>–1.0, 10^-7</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>–1.1, 10^-6</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7.1, 10^-5</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>7.5, 10^-5</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>1.5, 10^-4</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>6.7, 10^-8</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>6.7, 10^-8</td>
</tr>
<tr>
<td>Medications (variables considered in models a, b, c and d)</td>
<td></td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>–1.1, 10^-6</td>
</tr>
<tr>
<td>Clinical severity (variables considered in models a and c)</td>
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<tr>
<td>MDRS</td>
<td>2.9, 10^-8</td>
</tr>
<tr>
<td>mRS</td>
<td>–5.7, 10^-7</td>
</tr>
<tr>
<td>MRI markers (variables considered in models b and d)</td>
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</tr>
<tr>
<td>Mean-ADC</td>
<td>–4.6, 10^-7</td>
</tr>
<tr>
<td>Volume of LV</td>
<td>–4.4, 10^-7</td>
</tr>
<tr>
<td>Volume of WMH</td>
<td>8.7, 10^-8</td>
</tr>
<tr>
<td>Number of CM</td>
<td>–5.9, 10^-7</td>
</tr>
</tbody>
</table>

The variables used for multivariate analysis in the different models are indicated in the table. HDL: high density lipoprotein, LDL: low density lipoprotein.

Relationship between mean surface area of sulci and MRI markers (Table 2, model d)

In multivariate analysis, the mean surface area of sulci was inversely related to age (ß = –1.2 10^-5, SE = 3.8 10^-6, P = 0.0018), with only a trend for mean-ADC (ß = –4.7 10^-5, SE = 2.4 10^-5, P = 0.055).

Relationships between the different sulcal metrics and parameters of global brain morphology

The mean depth of sulci was linearly related to BPF (ß = 1.8 10^-5; P < 0.0001) (Fig. 2) and inversely related to age (ß = –1.1 10^-10; P = 0.025). The mean surface area of sulci was also related to BPF (ß = 2.9 10^-5; P < 0.0001) and inversely related to age (ß = –9.1 10^-8; P = 0.0004).

Slopes of regression for depth and surface area of each pair of sulci showed a variable rate according to the cortical sulcus (cingulate: –3.31% of initial depth value per year; central: –0.13%; superior temporal: –0.45%; superior frontal: –0.19%). For each sulcus, surface area was also related to age at a variable rate (cingulate: –0.46% of initial surface area per year; central: –0.16%; superior temporal: –0.57%; superior frontal: –0.38%).

Finally, the mean depth of sulci was inversely related to vV (ß = –1.6 10^-6; P < 0.0001), as was the mean surface area (ß = –2.4 10^-4; P = 0.002). In this series, vV was also strongly correlated to BPF (correlation coefficient r = 0.83, P < 0.0001).

Analysis of additional data obtained using non-validated segmentation techniques

In the group of 15 patients with failure of the original procedure to obtain a complete dataset, alternate methods were used to obtain the maximum number of segmented sulci. This was performed using multiple individual adjustments (tests of different thresholds for segmentation, change of step order in the procedure, modifications of algorithms for bias correction). After these individual adjustments, cortical sulci were accurately delineated in 13/15 patients (eight sulci (n = 5 patients), seven sulci (n = 4), five sulci (n = 2), four sulci (n = 1), two sulci (n = 1)). In two cases, the procedure failed to reconstruct and delineate any sulcus. Failures of the method to recognize sulci, despite multiple individual adjustments, were essentially related to the inability to detect boundaries between tissue classes resulting...
in reconstruction of an exceeding number of branches for each sulcus.

When the incomplete data from these 13 additional subjects were considered together with the previous results in the analysis of each individual sulcus, the depth of cingular sulcus was found significantly associated not only with vLL ($\beta = -3.6 \times 10^{-7}$, $SE = 1.2 \times 10^{-7}$, $P = 0.003$) but also with mean ADC ($\beta = -3.2 \times 10^{-7}$, $SE = 1.1 \times 10^{-7}$, $P = 0.004$). All the other results remained unchanged.

**Discussion**

This is the first study of 3D morphological changes occurring at the cortical level in CADASIL, a model of SVDB. The results show that important variations in cortical morphology are present in CADASIL and that they are strongly correlated with both the clinical status and the global volumetric brain changes. Indeed, depth and surface area of four easily identified sulci, measured on each hemisphere, were found to be strongly correlated with both cognitive and disability scales, independently of age and potential confounders. In addition, these parameters were strongly correlated with the reduction of the global brain volume and to the enlargement of cerebral ventricles progressing with age in this disorder (Peters et al., 2006; Jouvent et al., 2007). These results strongly support that both the depth and surface area of cortical sulci may accurately reflect the progression of the disease.

Cortical morphological changes have been previously observed during normal ageing. Using the same methodology, Kochunov et al. (2005) observed a reduction of sulcal depth with ageing in subjects ranging from 20 to 82 years, in agreement with other authors (Magnotta et al., 1999). As in our study, these cortical morphological changes were parallel to the global brain volume changes (Mueller et al., 1998; Courchesne et al., 2000; Sowell et al., 2003). In CADASIL, the rate of cerebral atrophy observed over two years is about two to three times higher than that of healthy individuals (Peters et al., 2006). Jouvent et al. recently showed that the increase in subcortical tissue lesions in this disease, particularly the accumulation of LL and spreading of microstructural loss, is associated with this accelerated cerebral atrophy (Jouvent et al., 2007). In the present study, the reduction in sulcal depth was found independent of age and strongly associated with the load of LL and increase of diffusion, which suggests that it also may result from the accumulation of macro and micro-structural cerebral tissue.

![Fig. 2](image_url)

**Fig. 2** Comparative 3D MRI results obtained in two patients. Left: 24-year-old patient with few white matter lesions, slight cortical and subcortical atrophy with deep sulci. Right: 69-year-old patient with a large amount of white-matter lesion, severe subcortical and cortical atrophy, and small sulci. The results of the study suggest that the effect of subcortical lesions largely exceeds that of age on the cortical morphological changes.
loss at the subcortical level. These results are in line with the observation of a reduction of cortical thickness associated with the extension of subcortical tissue lesions reported in a small sample of subjects with sporadic hypertension-related microangiopathy (Preul et al., 2005).

In contrast, the surface area of cortical sulci appeared mainly driven by age and not by the load of subcortical lesions. Since the surface area of sulci proceeds from both the length and depth of sulci, this result may indicate that the height and length of the corresponding cortical gyri may be affected in different proportion by age and by the accumulation of subcortical brain lesions. In contrast to normal ageing, the distribution of lesions in CADASIL mainly involve projecting fibres originating from the deep regions of the brain, with relative sparing of the U and inter-cortical white-matter fibres (Okeda et al., 2002). This may account for a different impact of age and of subcortical lesions on cortical morphology. It is of note that an independent gender effect was also detected on the mean depth of cortical sulci in the present study. A cross-sectional study in CADASIL has shown a negative effect of male sex on brain volume using the SIENAX method, a technique highly sensitive to cortical shrinkage (Peters et al., 2006). However, another study in CADASIL using a different method of brain volume measurement did not confirm this result (Jouvent et al., 2007). Another hypothesis to explain the absence of relationship between the mean sulcal area and the amount of subcortical lesions may be also related to the larger inter-individual variability of this measure in comparison to the calculation of sulcal depth, although the validation procedure confirmed the robustness of both measurements.

Regional analyses of sulcal depth suggested that the cortical surface area is not affected in a homogeneous fashion during the course of CADASIL. In normal ageing, the change in depth of the different sulci is highly variable. The central sulcus is the least affected, the superior temporal, the most affected (Kochunov et al., 2005). We observed the similar phenomenon in our sample, except for the cingulate and superior frontal sulci, which exhibited steeper decline. Moreover, depth of the cingulate sulcus was strongly and independently associated with the volume of LL, while that of superior frontal sulcus was related to mean-ADC values. In contrast, no significant effect of tissue lesions was detected on the depth of the central and superior temporal sulci. In addition, independent effects of male sex and hemispheric side were detected at the regional level. These data suggest that all cortical sulci may not be equally affected by the accumulation of subcortical lesions in CADASIL. The atrophy process may predominate in the anterior part of the brain and additional factors such as sex or laterality may also influence the regional distribution of cortical atrophy. In CADASIL, subcortical lesions are usually more severe in the frontal white-matter and basal ganglia than in posterior areas (Viswanathan et al., 2006b).

An important limitation of this study is that the delineation of sulci was not obtained using the original and validated procedure in 15 subjects who had the most extensive white-matter lesions. However, using alternate algorithms with multiple individual adjustments, additional sulci were reconstructed with high accuracy in 13 additional cases. These new data did not alter our primary findings. Measurement of the depth of cortical sulci in the present study also differs from previously reported mean sulcal depth in healthy subjects (Kochunov et al., 2005, 2008). We chose to calculate the maximum sulcal depth because this parameter is a reliable and highly reproducible measure. In contrast to the mean sulcal depth, it is independent of the number and length of branches identified for each sulcus, thus precluding measurement bias due to sulci identification errors. There is also growing evidence that the deepest parts of sulcal folds correspond to the most stable portions of sulci with the least inter-individual variability (Regis et al., 2005; Lohmann et al., 2007). The results confirm the high value of this parameter, which was found strongly related to both clinical status and other imaging parameters of the disease. In the present study, BPF was not used as a covariate in statistical analysis due to its linearity with sulci measurements. For this reason, the different correlates between sulci parameters and global atrophy measurements remain difficult to highlight. Further studies are also needed to compare lobar atrophy measures, which were not obtained in this study, and sulci measurements. Finally, in this study, we restricted measurements to four large sulci and therefore we cannot exclude that different relationship with subcortical lesions and clinical variables exist for other sulci in CADASIL. This is however unlikely due to the strong and similar effects detected on the different brain sulci parameters and to the strong relationships with the global shrinkage of the brain.

In conclusion, the results obtained in a population of CADASIL patients show that important modifications are observed at the cortical surface and are associated with the accumulation of subcortical lesions. The depth of sulci (reflecting the height of the corresponding gyri) was found to be strongly associated with the accumulation of subcortical lesions while the modifications of their surface area appear mainly driven by age. Apoptosis of cortical neurons has been reported in CADASIL patients in association with the severity of axonal loss in the underlying white-matter (Viswanathan et al., 2006a). The decrease of depth of cortical sulci may reflect both the reduction of axons underlying the gyral crowns and thinning of the cortical mantle caused by neuronal cortical apoptosis. Additional and follow-up studies are warranted to further study the magnitude and regional pattern of these morphological cortical changes in CADASIL, to determine their mechanisms and to investigate if such changes are also present and similar in other cerebral SVDB.

Acknowledgements

The authors acknowledge E. Vicaut and C. Boutron for their help and support in the building of the clinical and MRI
database, M. Boukobza and D. Reizine who participated in the MRI examination of patients. This work was supported by PHRC grant AOR 02-001 (DRC/APHP) and performed with the help of ARNEVA (Association de Recherche en Neurologie VAsculaire), Hôpital Lariboisière, France. E.J. was supported by a grant from the ‘Journées de Neurologie de Langue Française, France’. The study was also made possible with the sponsorship of Bouygues SA.

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