Strategic role of frontal white matter tracts in vascular cognitive impairment: a voxel-based lesion-symptom mapping study in CADASIL

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Cerebral small vessel disease is the most common cause of vascular cognitive impairment. It typically manifests with lacunar infarcts and ischaemic white matter lesions. However, little is known about how these lesions relate to the cognitive symptoms. Previous studies have found a poor correlation between the burden of ischaemic lesions and cognitive symptoms, thus leaving much of the variance in cognitive performance unexplained. The objective of the current study was to investigate the relationship between the location of subcortical ischaemic lesions and cognitive symptoms in small vessel disease. We applied a voxel-based lesion-symptom mapping approach to data from 215 patients with CADASIL, a genetically defined small vessel disease with mutations in the NOTCH3 gene. All patients were examined by magnetic resonance imaging and comprehensive neuropsychological testing. Lacunar lesions and white matter lesions were segmented on three-dimensional T1 and fluid-attenuated inversion recovery sequences, respectively. One hundred and forty-five subjects had a total of 854 lacunar lesions (range 1–13 per individual). The normalized volume of white matter hyperintensities ranged from 0.0425% to 21.5% of the intracranial cavity. Significant clusters for cognitive performance were detected for both lacunar lesions and white matter hyperintensities. The most prominent results were obtained on a compound score for processing speed, the predominantly affected cognitive domain in this group of patients. Strategic locations included the anterior parts of the thalamus, the genu and anterior limb of the internal capsule, the anterior corona radiata and the genu of the corpus callosum. By combining the lesion-symptom mapping data with information from a probabilistic white matter atlas we found that the majority of the processing speed clusters projected on the anterior thalamic radiation and the forceps minor. In multivariate models that included demographic parameters, brain atrophy and the volume of ischaemic lesions, regional volumes of lacunar lesions and white matter hyperintensities in the anterior thalamic radiation predicted performance in processing speed tasks, whereas there was no independent contribution of the global volume of ischaemic lesions. These observations emphasize the importance of lesion location for both lacunar and ischaemic white matter lesions. Our findings further highlight the anterior thalamic radiation as a major anatomical structure impacting on processing speed. Together these findings provide strong support for a central role of frontal-subcortical circuits in cerebral small vessel disease and vascular cognitive impairment.
Introduction

Vascular cognitive impairment is the second most common cause of dementia following Alzheimer’s disease. Vascular cognitive impairment has been associated with various lesion patterns including multiple infarcts, single strategic infarcts and incomplete ischaemic lesions mainly in the cerebral white matter (Román et al., 2002; O’Brien et al., 2003; Selnes and Vinters, 2006). However, the exact relationship between these lesions and cognitive impairment is still strongly debated.

MRI and autopsy studies have demonstrated an impact of the total burden of ischaemic lesions on cognitive status. An association between lesion volumes and cognitive performance has been demonstrated for infarcts (Erkinjuntti et al., 1988; Tatemichi et al., 1993; Pohjasvaara et al., 1998), lacunar infarcts (Mungas et al., 2005; Liem et al., 2007) and white matter lesions (O’Brien et al., 2002; Prins et al., 2005). In general, however, correlations between volumetric measures and cognitive performance have been modest leaving much of the clinical variance unexplained.

Another increasingly recognized factor is lesion location. Thus, for example, lacunar infarcts in the thalamus and basal ganglia were found to have a larger impact on cognition than infarcts in the deep white matter (Gold et al., 2005). In the Rotterdam Scan Study, periventricular but not subcortical white matter lesions were associated with both cognitive function (de Groot et al., 2000) and cognitive decline during follow-up (de Groot et al., 2002). This finding, although still somewhat controversial (Smith et al., 2000; Debette et al., 2007; Delano-Wood et al., 2008), has been attributed to a disruption of functionally important neuronal tracts traversing the periventricular and deep white matter.

Extending these observations, recent studies have focused on major cognitive domains. In the Rotterdam Scan Study, thalamic infarcts were associated with a decline in memory performance, whereas non-thalamic infarcts were associated with a decline in psychomotor speed (Vermeer et al., 2003). These relationships were further influenced by the presence of additional infarcts adding to the notion that there is an interplay between the burden of ischaemic lesions and their spatial distribution in determining cognitive status (Saczynski et al., 2009).

Patients with vascular cognitive impairment often show deficits of attention and executive function with slowing of information processing (Selnes and Vinters, 2006). This profile has been related to the frequent occurrence of vascular lesions in brain structures harbouring frontal-subcortical circuits (Cummings, 1989; Chui, 2005) and is particularly prominent in patients with cerebral small vessel disease, the most common cause of vascular cognitive impairment (Román et al., 2002; O’Brien et al., 2003; Prins et al., 2005; Jokinen et al., 2009).

Small vessel disease typically manifests with two types of lesions: cavitating lacunar lesions and incomplete ischaemic lesions that are hyperintense on fluid-attenuated inversion recovery and T2-weighted MRI. The latter are typically located within the white matter and are thus termed white matter hyperintensities but may likewise involve the deep grey matter (van Straaten et al., 2003; Jacqmin et al., 2010). The same changes are also found in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL), a hereditary small vessel disease caused by mutations in the NOTCH3 gene (Opferk, 2004; Chabriat et al., 2009). Because of an early onset, age-related pathologies, such as Alzheimer-type changes, are uncommon in these patients. Thus, CADASIL has become a model for studying the mechanisms of small vessel disease and vascular cognitive impairment, in particular (Peters et al., 2005; Charlton et al., 2006; Dichgans et al., 2008; Jouvent et al., 2008; Chabriat et al., 2009).

In this study, we explored the role of strategic lesions for cognitive deficits in CADASIL. We hypothesized that strategic locations can be detected for both lacunar lesions and white matter hyperintensities and that locations may vary between cognitive domains. We further speculated that strategic locations for lacunar lesions and white matter hyperintensities affect similar brain regions or white matter tracts. Finally, we hypothesized that the total burden of lesions within strategic white matter tracts may be more predictive for cognitive performance than the global burden of lacunar lesions and white matter hyperintensities in the brain. To address these questions in a systematic manner, we used a hypothesis-free voxel-based lesion-symptom mapping approach.

Materials and methods

Study cohort and neuropsychological testing

Patients with CADASIL (n = 320) from an ongoing prospective study (Klinikum Großhadern, University of Munich, Germany and Hopital Lariboisière, Paris, France) were evaluated for inclusion. In all subjects, the diagnosis had been confirmed either by skin biopsy or genetic testing (Joutel et al., 1997; Peters et al., 2005). Neuropsychological testing was carried out using the following tests: Trail Making Test Parts A and B; block design, digit span; similarities; verbal fluency; free recall; and delayed free recall. Raw test scores were transformed into age- and education-corrected Z-scores based on reference values obtained from healthy subjects (Van der Linen et al., 1993; TROYER, 2000; Tombaugh, 2004; Wechsler, 2006).

Fifty patients were excluded based on their MRI scans for the following reasons: (i) insufficient image quality such as motion artefacts (n = 15); (ii) territorial infarctions (n = 3); and (iii) difficulties in registering images to standard space (n = 32; see below). Thus, images from 270 subjects were available in standard space. Of those, 55 patients had to be excluded because of failure to adequately perform or complete all neuropsychological tests. These patients did not differ significantly from the remaining subjects in terms of normalized white matter hyperintensities volume (Mann–Whitney U-test; P = 0.085) but had slightly higher normalized lacunar lesion volume.

Keywords: vascular cognitive impairment; voxel-based lesion-symptom mapping; lacunes; white matter hyperintensities; CADASIL

Abbreviations: CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
Lesion maps were generated using custom 2D and 3D image editing tools provided by BioClinica SAS. Lacunar lesion maps were created using a slightly modified version of our previously published protocol (Viswanathan et al., 2007): hypointense lesions on the T1-weighted images with a signal identical to CSF, sharp delineation and a diameter >2 mm were segmented as lacunar lesions. Virchow–Robin spaces were excluded by size <2 mm and their typical orientation along perforating vessels or perpendicular to the brain surface (Doubal et al., 2010). Particular attention was paid to brain regions typically containing Virchow–Robin spaces (Kwee and Kwee, 2007). In difficult cases, decisions were reached by consensus between two or more experienced raters. Lesions hyperintense on fluid-attenuated inversion recovery images were labelled white matter hyperintensities although some of these lesions also affected the subcortical grey matter. White matter hyperintensity maps were generated as previously described (Viswanathan et al., 2006).

The intracranial cavity (brain parenchyma plus CSF space) was determined using an automated 3D image segmentation algorithm on the T2 sequence followed by manual correction. Lesion volumes were calculated from lesion maps and divided by intracranial cavity for normalization. The intra- and interrater reliability for these procedures has been shown to be high (Viswanathan et al., 2006, 2010). The overlap of lesion masks between raters as judged by the Dice coefficient was good for lacunar lesion masks (0.88) and excellent for white matter hyperintensities (0.98).

Brain volume was estimated from native T1 images with Sienax (Smith et al., 2001, 2002), part of the FMRIB software library (Smith et al., 2004; Woolrich et al., 2009). Sienax extracts brain and skull images from whole-head input data to calculate brain volume (Smith, 2002). Results were manually checked and parameters optimized if necessary. Brain parenchymal fraction was calculated by dividing total brain volume by intracranial cavity.

Tools from the FMRIB software library (most recent version, August 2008) were used for all subsequent processing steps. For registration to standard space, a lesion masking approach was applied to enhance registration quality and to better preserve anatomical structures (Brett et al., 2001). In brief, cost-function masks were created by subtracting lesion maps from brain masks in T1 space. Linear (FMRIB software library flirt) and non-linear (FMRIB software library fnirt) registration of T1 images were done with standard parameters to a 1 mm Montreal Neurological Institute (MNI) 152 template provided within the FMRIB software library. Rigorous quality checks were done at all steps by superimposing results onto the target image. Where needed, parameters were adjusted to optimize the registration process. Thirty-two subjects were excluded because of pronounced image distortion mostly due to atrophy. After quality control of T1 images in MNI space, the warp fields were used to co-register corresponding lesion maps to a 2-mm MNI template. To correct for small registration errors, modest smoothing (mean filtering, Gaussian kernel 4 mm, threshold 0.5) was applied to lacunar lesion maps.

### Voxel-based lesion-symptom mapping

Analyses were done on compound scores for major cognitive domains. Compound scores were defined by principal component analysis (confirmatory analysis). Principal component analysis seeks for combinations of variables in order to extract the maximum variance from the data set. These combinations are represented by factors. A three-factor model was used to describe the data and a standard procedure to maximize factor loadings (varimax rotation) was applied. Only neuropsychological tests clearly loading on one of the three factors were considered for the generation of compound scores. Non-parametric mapping (most recent version, April 2010) was used to relate lesion location to cognitive performance (Rorden et al., 2007) (settings: Brunner–Munzel test, 4000 permutations for univariate analysis). Voxels affected in less than four subjects were not considered for analysis. Correction for multiple testing was achieved by permutation generated family-wise error (FWE) thresholds ($P_{\text{FWE}} < 0.01$ for white matter hyperintensities) or false detection rate ($P_{\text{FDR}} < 0.05$ for lacunar lesions). Voxels reaching statistical significance were projected on major white matter tracts as identified on a probabilistic white matter tract atlas (Hua et al., 2008) provided within the FMRIB software library (Johns Hopkins University-International Consortium for Brain Mapping (JHU-ICBM) tracts, maximum probability map). Images are displayed according to neurological convention (right side displayed on the right).

### Region of interest-based multiple regression analysis

We used information from the white matter parcellation atlas (maximum probability map, thresholded at a probability of 0.1) to create regions of interest for major white matter tracts in MNI space. These regions of interest were then used to calculate regional volumes in standard space for lacunar lesions and white matter hyperintensities within specific white matter tracts. Regional volumes were entered as independent variables in a step-wise multiple linear regression model (SPSS, version 19).

### Results

Demographic, clinical and MRI characteristics of the study cohort are provided in Table 1. The median normalized lesion volume (in percentage of intracranial cavity) was 0.00526 for lacunar lesions (interquartile range 0.0219) and 5.54 for white matter hyperintensities (interquartile range 5.96).

### Lesion prevalence maps

Overall, there were 854 lacunar lesions present in 145 subjects (mean number per patient in the entire cohort of 215 patients = 4, range 0–13). As illustrated by the lesion prevalence maps, frequent locations included the thalamus, the anterior limb of the internal capsule, anterior parts of the striatum and globus pallidus, the centrum semiovale and the pons (Fig. 1A). The anatomical distribution of lacunar lesions was similar between subgroups stratified for the normalized lacunar lesion volume (Supplementary Fig. 1).
White matter hyperintensities were detected in all subjects. They were found in the majority of voxels representing white matter and several voxels representing central grey matter (Fig. 1B). White matter hyperintensities were most prevalent in the periventricular and deep white matter and were less prevalent in the internal capsule and central grey matter. The overall pattern was highly symmetrical between the left and right hemisphere with a spread towards subcortical white matter as the overall volume of lesions increased (Supplementary Fig. 2).

Cognitive profile and major cognitive domains

Figure 2A shows the cognitive profile in the entire study sample. Principal component analysis of individual test scores revealed three factors explaining 88% of raw score variance. Factor 1 (3% variance) was determined by timed tests requiring visual executive functions (Trail Making Test parts A and B, block design). Factor 2 (33% variance) is a verbal memory factor, determined largely by immediate and delayed verbal recall, with minor contribution of verbal fluency and verbal similarities. Factor 3 (18% variance) was marked by digit span, again with minor contribution of verbal fluency and verbal similarities. All subsequent analyses were done on scores derived from the principal component analysis: a compound score reflecting processing speed (PC1), a compound score for memory (PC2) and a third score represented by the digit span (PC3) (Fig. 2A).

Figures 2A and 2C show the cognitive profiles in subgroups stratified for the volume of lacunar lesions and white matter hyperintensities, respectively. Between-group differences with regard to lesion volumes were found for processing speed (multivariate analysis of variance lacunar lesions: P = 0.001; white matter hyperintensities: P = 0.01) and memory (lacunar lesions: P < 0.001; white matter hyperintensities: P < 0.05) but not for the digit span.

Voxel-based lesion-symptom mapping

Processing speed

Non-parametric voxel-based lesion-symptom mapping for the processing speed score revealed significant clusters for both lacunar lesions and white matter hyperintensities following correction for testing of multiple voxels (Fig. 3A and 3B, Supplementary Table 1).

For lacunar lesions significant clusters were found bilaterally in the anterior part of the thalamus (extending to the capsular genu on the right) and the anterior limb of the internal capsule (Fig. 3A; MNI z = 0–15). Additional clusters were seen in the left genu of the corpus callosum (z = 0 and 5) and the left anterior corona

### Table 1 Characteristics of the study cohort (n = 215)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Study cohort</th>
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<tbody>
<tr>
<td>Demographic characteristics</td>
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</tr>
<tr>
<td>Age, mean (SD) (years)</td>
<td>47.9 (10.7)</td>
</tr>
<tr>
<td>Education, mean (SD) (years)</td>
<td>10.8 (3.3)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>127 (59.1)</td>
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<tr>
<td>Clinical features</td>
<td></td>
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<tr>
<td>Symptomatic, n (%)</td>
<td>197 (91.6)</td>
</tr>
<tr>
<td>Prior clinically apparent stroke, n (%)</td>
<td>128 (59.5)</td>
</tr>
<tr>
<td>Years since first stroke, median (IQR)</td>
<td>4.1 (7.8)</td>
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<tr>
<td>Migraine history, n (%)</td>
<td>105 (48.8)</td>
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<tr>
<td>History for depression, n (%)</td>
<td>80 (37.2)</td>
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<tr>
<td>Vascular risk factors</td>
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<tr>
<td>Current smoker</td>
<td>49 (22.8%)</td>
</tr>
<tr>
<td>Smoking history</td>
<td>75 (34.9%)</td>
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<tr>
<td>Hypertension</td>
<td>43 (20.0%)</td>
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<tr>
<td>Hypercholesterolaemia</td>
<td>72 (33.5%)</td>
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<tr>
<td>Diabetes</td>
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<tr>
<td>Clinical scores</td>
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<tr>
<td>MDRS, median (IQR)</td>
<td>141 (7)</td>
</tr>
<tr>
<td>Modified Rankin scale, median (IQR)</td>
<td>0 (1)</td>
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<tr>
<td>Modified Rankin scale &gt; 2</td>
<td>15 (7.0%)</td>
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<tr>
<td>NIH stroke scale, median (IQR)</td>
<td>0 (1)</td>
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<tr>
<td>Barthel index, median (IQR)</td>
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<tr>
<td>Imaging characteristics, mean (SD) (%)</td>
<td></td>
</tr>
<tr>
<td>Normalized lacunar lesion volume</td>
<td>0.0225 (0.047)</td>
</tr>
<tr>
<td>Normalized WMHV</td>
<td>6.75 (4.9)</td>
</tr>
<tr>
<td>Brain parenchymal fraction</td>
<td>83.6 (5.3)</td>
</tr>
</tbody>
</table>

IQR = interquartile range; MDRS = Mattis dementia rating scale; WMHV = white matter hyperintensities volume.
radiata ($z = 20$). When adding normalized lacunar lesion volume as a covariate only the thalamic clusters remained significant.

For white matter hyperintensities, significant clusters were found bilaterally in the genu of the corpus callosum ($z = 0–15$), the anterior limb of the internal capsule ($z = 0–15$) and the anterior corona radiata ($z = 15$) (Fig. 3A). Significant clusters were further detected in the posterior limb of the left internal capsule extending to the centrum semiovale ($z = 10–25$) and the splenium ($z = 15–25$). Several of these clusters remained significant when adding normalized white matter hyperintensity volume as a covariate.

**Memory**

For the memory score significant clusters were found for white matter hyperintensities predominantly in the splenium of the corpus callosum (Fig. 3C, $z = 10–20$). Several voxels remained significant when adding normalized white matter hyperintensity volume as a covariate.

**Digit span**

No significant voxels were identified for digit span.

**Identification of strategically relevant white matter tracts**

To examine the spatial relationship between strategic lesions and major white matter tracts, we projected significant clusters from the lesion-symptom mapping on a JHU-ICBM white matter atlas registered to MNI space. As shown in Fig. 3B, the majority of processing speed clusters projected on the anterior thalamic radiations, the forceps minor, the forceps major and the left corticospinal tract. The most prominently involved structures were the anterior thalamic radiation (bilateral clusters for both lacunar lesions and white matter hyperintensities) and the forceps minor (bilateral clusters for white matter hyperintensities, unilateral cluster for lacunar lesions). Clusters for the memory score mostly projected on the forceps major (Fig. 3C).

**Region of interest-based regression models for processing speed**

In a last step, we assessed whether the cumulative burden of lesions within strategic white matter tracts is more predictive for cognitive performance than the global burden of lacunar lesions and white matter hyperintensities in the brain. Given the prominent role of processing speed and of frontal white matter tracts (anterior thalamic radiation and forceps minor, Fig. 3B) we focused on these components. Regional volumes of lacunar lesions and white matter hyperintensities projecting on the anterior thalamic radiation and forceps minor were measured in standard space (Fig. 4) and entered into step-wise multiple regression models with processing speed as dependent variable. In a model that included both regional and global lesion volumes, lacunar lesions in the anterior thalamic radiation explained most of the variance (adjusted $R^2 = 0.15$) followed by white matter hyperintensities in the anterior thalamic radiation and lacunar lesions in the forceps minor (Table 2). Global lesion volumes and white matter hyperintensities in the forceps minor did not contribute to the model. After adding brain parenchymal fraction, age, sex and years of formal education to the model, brain parenchymal fraction explained most of the variance, followed by the regional volumes of lacunar lesions and white matter hyperintensities in the anterior thalamic radiation. None of the other variables contributed to the model.
Discussion

This study demonstrates a possible link between the distribution of subcortical ischaemic lesions and the profile of cognitive symptoms in patients with CADASIL, a genetic cause of small vessel disease and vascular cognitive impairment.

Using a voxel-based approach we identified several locations for lacunar lesions and white matter hyperintensities that were significantly associated with performance in distinct cognitive domains. The most prominent results were obtained for processing speed, the predominantly affected domain in our patients. The results on lacunar lesions and white matter hyperintensities are

Figure 3 Voxel-based lesion-symptom mapping results for processing speed (A and B) and memory (C) in MNI space. (A) Significant clusters for processing speed after non-parametric mapping and correction for multiple testing. Orange indicates voxels remaining significant after adding normalized LL volume and normalized white matter hyperintensity (WMH) volume as a covariate. (B) Significant clusters for lacunar lesions (red) and white matter hyperintensities (green) projected on major white matter tracts (JHU-ICBM-DTI atlas). Depicted are the forceps minor, the anterior thalamic radiation, the forceps major and the corticospinal tract. (C) Significant clusters (white matter hyperintensities) for memory. Voxels that remained significant after correction for global normalized white matter hyperintensity volume are depicted in orange. The statistical maps are superimposed onto the MNI T1 template. There were no significant clusters in slices outside the region shown in A–C.
complementary and identify the anterior thalamic radiation and forceps minor as functionally important anatomical structures. A strategic role of the anterior thalamic radiation is further suggested by the multivariate models showing that the volume of lacunar lesions and white matter hyperintensities projecting on this white matter tract independently predict cognitive deficits. Together, these observations highlight the role of frontal-subcortical circuits in small vessel disease and vascular cognitive impairment.

To our knowledge, this is the first lesion-symptom mapping study on subcortical ischaemic lesions and cognitive performance using voxel-based methods. Our findings on lacunar lesions and processing speed add to earlier reports on patients who developed dementia in the context of small infarcts in the thalamus (Kalashnikova et al., 1999; Auchus et al., 2002; Szirmai et al., 2002), genu (Tatemichi et al., 1992) and anterior limb (Kalashnikova et al., 1999) of the internal capsule and anterior part of the corpus callosum (Auchus et al., 2002). In fact, the processing speed clusters for lacunar lesions match remarkably well with locations previously reported to be associated with strategic infarct dementia (Tatemichi et al., 1995).

In the Rotterdam Scan Study, silent thalamic infarcts were associated with a decline in memory, whereas non-thalamic infarcts were associated with a decline in psychomotor speed (Vermeer et al., 2003, 2007; Gold et al., 2005). We found no significant clusters for lacunar lesions and memory, possibly because memory was relatively preserved in our cohort. However, the results on processing speed broadly agree with those from the Rotterdam Scan Study while providing a more detailed account of infarct locations associated with processing speed.

A major finding of this study was that white matter hyperintensities in distinct, partially overlapping brain regions also associate with processing speed. The identified clusters extend on earlier sporadic reports, which found processing speed to be associated with white matter hyperintensities in the caudate nucleus, internal capsule and thalamus (O’Brien et al., 2002; Burton et al., 2003). However, these studies were small, hypothesis driven and did not control for the total burden of lesions. In the current study, many of the white matter hyperintensity clusters for processing speed remained significant when controlling for lesion volumes. We, therefore, hypothesize that these clusters represent true strategic locations. In support of this, there was considerable overlap between processing speed clusters for white matter hyperintensities and lacunar lesions with regard to functional anatomical structures such as the anterior thalamic radiation.

Some of the white matter hyperintensity clusters for processing speed projected on the left corticospinal tract. This finding likely reflects the effects of motor impairment on our processing speed tasks, all of which involved manual skills. In fact, we feel that the corticospinal tract clusters can be viewed as an internal validation of the voxel-based lesion-symptom mapping. However, this could not be formally assessed as we did not control for hand motor function. Also, we cannot exclude the possibility that motor impairments contributed to some of the other clusters.

We also found single clusters for white matter hyperintensities and memory in the splenium of the corpus callosum. There is some evidence for a role of the splenium in episodic memory (Voeneskos et al., 2010), whereas there are little data on verbal memory, which was the main contributor to our compound score. However, we feel the findings on memory must be interpreted cautiously since memory was relatively preserved in our cohort. This might also explain why we found no significant clusters for memory and lacunar lesions.

Adding information from the JHU-ICBM white matter atlas we found that many of the processing speed clusters project on the anterior thalamic radiation and forceps minor. As a major white matter tract, the anterior thalamic radiation carries reciprocal projections between the thalamus, prefrontal cortex and striatum, which participate in prefrontal-subcortical circuits (Behrens et al., 2003). There is a broad literature suggesting an involvement of these circuits in processing speed and executive functioning (Mega and Cummings, 1994; Tekin and Cummings, 2002). Our findings

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**Table 2 Step-wise multiple linear regression analysis on processing speed**

<table>
<thead>
<tr>
<th>Step</th>
<th>Variable</th>
<th>$P$</th>
<th>Standardized $\beta$</th>
<th>Adjusted $R^2$</th>
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</thead>
<tbody>
<tr>
<td>Model A</td>
<td>1</td>
<td>LLV (anterior thalamic radiation)</td>
<td>$&lt;0.000$</td>
<td>$-0.277$</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>WMHV (anterior thalamic radiation)</td>
<td>$&lt;0.000$</td>
<td>$-0.258$</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>LLV (forceps minor)</td>
<td>$&lt;0.002$</td>
<td>$-0.195$</td>
</tr>
<tr>
<td>Model B</td>
<td>1</td>
<td>Brain parenchymal fraction</td>
<td>$&lt;0.000$</td>
<td>0.267</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>LLV (anterior thalamic radiation)</td>
<td>$&lt;0.000$</td>
<td>$-0.265$</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>WMHV (anterior thalamic radiation)</td>
<td>$&lt;0.001$</td>
<td>$-0.213$</td>
</tr>
</tbody>
</table>

a Independent variables: LLV (global), LLV (anterior thalamic radiation), LLV (forceps minor), WMHV (global), WMHV (anterior thalamic radiation), WMHV (forceps minor).

b Variables as in Model A, with addition of brain parenchymal fraction, age, sex and formal education (years).

LLV = lacunar lesion volume; WMHV = white matter hyperintensities volume.
add to this concept while emphasizing a strategic role of subcortical ischaemic lesions. A role of the anterior thalamic radiation in processing speed is also suggested by a recent study on patients with first-episode psychosis (Pérez-Iglesias et al., 2010). Likewise, our finding of significant clusters in the forceps minor agree with data showing that microstructural integrity of the genu of the corpus callosum influences interhemispheric processing speed (Schulte et al., 2005).

In regression models accounting for global and regional measures of disease burden, regional volumes of lacunar lesions and white matter hyperintensities in the anterior thalamic radiation both had an independent influence on processing speed. In contrast, there was no independent contribution of the global volume of lacunar lesions and white matter hyperintensities when regional volumes were included in the model. This finding may help resolve some of the controversy between studies that have emphasized the importance of lesion location versus lesion volumes (Gold, 2009). Our data suggest that both aspects are important but that the cumulative volume of lesions within specific functional networks may be clinically more relevant than the total volume of lesions within the brain. Still, the explained variance in our models is only modest, indicating a potential role of other factors. Such factors might include microstructural damage within brain tissue appearing normal on T₂-weighted images (O’Sullivan et al., 2005) or individual compensatory mechanisms such as cognitive reserve, which has been shown to modify the relationship between pathology and cognitive performance (Brickman et al., 2009).

The lesion prevalence maps demonstrate clear predilection sites for lacunar lesions and white matter hyperintensities with an early spread of lesions into anatomical structures found here to be strategically important. Frequent locations for lacunar lesions included the striatum, the internal capsule and the thalamus, whereas white matter hyperintensities tended to accrue in the periventricular white matter. This pattern matches with that reported for sporadic small vessel disease (Enzinger et al., 2006). It has been suggested that the cognitive profile of vascular cognitive impairment with frequent impairments of executive function and processing speed in part relates to the frequent spread of lesions into anatomical structures harbouring frontal-subcortical circuits (Cummings, 1989; Chui, 2007). Our study supports this concept while demonstrating a role for both lacunar lesions and white matter hyperintensities.

There are limitations to our study that should be considered. First, we might have missed functionally relevant locations because there were too few lesions. This is most obvious for lacunar lesions. Chances to detect significant associations were, therefore, higher in locations commonly affected in Cadasil, although the issue is likely to be less relevant for white matter hyperintensities, which were more widespread and exhibited higher lesion frequencies than lacunar lesions (Fig. 1). A significant proportion of patients had to be excluded because of difficulties in registering images or failure to complete all the neuropsychological tests. This, together with potential biases in patient recruitment, might have led to a selection of patients who were less impaired. Second, we cannot exclude errors associated with normalization and registration processes. However, we consider these errors to be small as all images were rigorously controlled by visual inspection. Finally, we did not include other imaging modalities such as diffusion tensor imaging, which are more sensitive in capturing subtle structural abnormalities (O’Sullivan et al., 2004; Turken et al., 2008; Pérez-Iglesias et al., 2010). Thus, effects from more widespread microscopic lesions might have been missed.

The main strengths of this study are the homogeneity of the sample, a large sample size and the hypothesis-free approach using voxel-based methods. Studies in typically older patients with sporadic small vessel disease are complicated by a high prevalence of comorbid age-related pathologies (Schneider et al., 2007), which may interfere with studying the mechanisms of vascular cognitive impairment. The average age in our patients was well below the age at which typical age-related causes of cognitive impairment commence. Thus, we are confident that our findings truly relate to the underlying small vessel disease.

In summary, we identified strategic locations for subcortical ischaemic lesions impacting on processing speed as a major cognitive aspect of vascular cognitive impairment. Significant clusters were found for both lacunar lesions and white matter hyperintensities. The results are complementary and identify the anterior thalamic radiation and the forceps minor as key anatomical structures. Taken together, our observations emphasize the role of frontal-subcortical circuits in subcortical ischaemic vascular disease and related cognitive impairment. Future studies in sporadic patients may show whether these findings are applicable to other types of small vessel disease.

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Supplementary material

Supplementary material is available at Brain online.

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