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# Impact of regional cortical and subcortical changes on processing speed in cerebral small vessel disease

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ABSTRACT

Slowed processing speed is common in elderly subjects and frequently related to cerebral small vessel disease. Previous studies have demonstrated associations between processing speed and subcortical ischemic lesions as well as cortical alterations but the precise functional–anatomical relationships remain poorly understood. Here we assessed the impact of both cortical and subcortical changes on processing speed by measuring regional cortical thickness and regional lesion volumes within distinct white-matter tracts. To limit confounding effects from age-related pathologies we studied patients with CADASIL, a genetic small vessel disease. General linear model analysis revealed significant associations between cortical thickness in the medial frontal and occipito-temporal cortex and processing speed. Bayesian network analysis showed a robust conditional dependency between the volume of lacunar lesions in the left anterior thalamic radiation and cortical thickness of the left medial frontal cortex, and between thickness of the left medial frontal cortex and processing speed, whereas there was no direct dependency between lesion volumes in the left anterior thalamic radiation and processing speed. Our results suggest that the medial frontal cortex has an intermediate position between lacunar lesions in the anterior thalamic radiation and deficits in processing speed. In contrast, we did not observe such a relationship for the occipito-temporal region. These findings reinforce the key role of frontal–subcortical circuits in cognitive impairment resulting from cerebral small vessel disease.



## 1. Introduction

Deficits in information processing speed are common in elderly subjects (Eckert, 2011; Salthouse, 2000) and a typical feature of vascular cognitive impairment (O'Brien et al., 2003). They are frequently related to cerebral small vessel disease (SVD) (Jokinen et al., 2009; Peters et al., 2005b; Prins et al., 2005), but the mechanisms are insufficiently understood.

Studies in healthy subjects and in patients with brain injury suggest a key role of frontal–subcortical circuits in information processing speed (Alexander et al., 2007; Chui, 2007; Cummings, 1993; Eckert, 2011; Stuss, 2011). In fact, recent MR imaging studies have shown that processing speed performance correlates with various measures in the frontal lobe including white matter integrity, white matter atrophy, and sulcal span (Bartzokis et al., 2010; Kochunov et al., 2010). These findings are complemented by data demonstrating an inverse relationship between cortical thickness in frontal brain regions and speed scores (Chee et al., 2009).

Processing speed deficits in SVD have been related to the presence of ischemic lesions in brain regions harboring frontal–subcortical circuits (Chui, 2007). In support of this, a recent voxel-based MRI lesion symptom mapping study on lacunar lesions (LL) and white matter hyperintensities (WMH) identified the anterior thalamic radiation and the forceps minor as strategic white matter tracts for processing speed deficits (Duering et al., 2011). Importantly however, this study did not account for cortical alterations.

Brain atrophy is now recognized as a major predictor of cognitive decline in SVD (Jokinen et al., 2012; Prins et al., 2005). A relationship

*Abbreviations:* SVD, small vessel disease; LL, lacunar lesions; WMH, white-matter hyperintensities; MFC, medial frontal cortex; OTC, occipito-temporal cortex; ATR, anterior thalamic radiation.

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with subcortical ischemic lesions is suggested by recent data showing that incident subcortical infarcts induce cortical atrophy in connected brain regions (Duering et al., 2012). However, the interactions between subcortical lesions and cortical atrophy, and their influence on cognitive symptoms remain largely unexamined (Jouvent et al., 2012; Seo et al., 2012).

We thus set out to combine measurements of cortical thickness with quantification of both LL and WMH within major white matter tracts. We hypothesized i) that deficits in processing speed are related to cortical thinning in frontal brain regions and ii) that thinning in these regions relates to the extent of ischemic lesions in frontal white matter tracts. To assess these relationships we used graph-based methods. To minimize potential confounding by unrecognized neurodegenerative disease we studied patients with CADASIL, an early-onset condition causing pure SVD (Chabriat et al., 2009; Peters et al., 2004).

## 2. Methods

### 2.1. Study cohort and neuropsychological testing

313 consecutive CADASIL patients from a two-center study (Klinikum Großhadern, University of Munich, Germany, and Centre Hospitalier Universitaire (CHU) Lariboisière, Paris, France) were evaluated for inclusion. In all subjects, the diagnosis was confirmed either by skin biopsy or genetic testing (Joutel et al., 1997; Peters et al., 2005a).

Patients were excluded from the study for the following reasons: territorial infarctions ($n = 3$), insufficient quality of T1-weighted images or problems with cortical surface analyses due to subcortical white-matter hyperintensities directly underneath the cortex ($n = 150$), missing data on neuropsychological measures ($n = 13$), or a combination of these reasons ($n = 49$). The final study sample included 98 patients (Table 1). Patients in the final sample were younger ($t = 7.34$, $p < 0.001$), had smaller volumes of LL ($t = 2.87$, $p < 0.005$) and WMH ($t = 8.23$, $p < 0.001$), and a larger brain parenchymal fraction, which is the total brain volume divided by the intracranial cavity ($t = 2.93$, $p < 0.005$).

Cognitive testing included the Mattis Dementia Rating Scale (Schmidt et al., 1994) as a global measure for cognitive performance across multiple cognitive areas. Processing speed was determined using a compound score derived from principle component analysis as previously described (Duering et al., 2011). This score included the timed measures of TMT-A, TMT-B and the block design test. Raw test scores were transformed into age- and education corrected Z-scores based on normative data from healthy subjects (Tombaugh, 2004; Troyer, 2000; Van der Linen et al., 1993; Wechsler, 2006). The mean of these three Z-scores formed the processing speed compound Z score.

**Table 1**
Characteristics of the study sample (n = 98).

| Demographic characteristics | Included (N = 98) | Excluded (N = 215) | Significance |
|---|---|---|---|
| Age, mean (SD, range) | 43.7 (9.6, 22–67) | 53.1 (10.8, 24–77) | $p < 0.001$ |
| Male sex, n (%) | 38 (38) | 105 (49) | ns |
| Vascular risk factors, n (%) | | | |
| Current smoker | 25 (26) | 35 (16) | ns |
| Smoking history | 33 (33) | 67 (31) | ns |
| Hypertension | 19 (19) | 42 (20) | ns |
| Hypercholesterolemia | 25 (26) | 91 (42) | $p < 0.01$ |
| Diabetes | 4 (4) | 3 (1) | ns |
| Clinical scores, median (IQR) | | | |
| Mattis Dementia Rating Scale | 142 (4) | 139 (16.25) | $p < 0.001$ |
| Modified Rankin scale | 0 (0.8) | 1 (2) | ns |
| Barthel index | 100 (0) | 100 (5) | ns |
| Imaging characteristics, mean (SD) [%] | | | |
| Normalized LL volume | 0.0164 (0.0315) | 0.0346 (0.0588) | $p < 0.01$ |
| Normalized WMH volume | 4.14 (2.69) | 8.82 (5.28) | $p < 0.001$ |
| Brain parenchymal fraction | 83.7 (4.91) | 81.4 (5.86) | $p < 0.01$ |

IQR = interquartile range, LL = lacunar lesion, WMH = white matter hyperintensities. Comparisons between the included and excluded samples were performed by chi-square statistics for categorical variables and *t*-test statistics for continuous variables.

### 2.2. Acquisition of MR images

MRI scans were performed on 1.5 Tesla systems: Siemens Vision (Munich) and General Electric Medical Systems Signa (Paris and Munich). Sequence parameters for the 3D T1 and fluid-attenuated inversion recovery protocols have previously been published (Jouvent et al., 2007) (Supplementary Table A.1).

### 2.3. Cortical thickness

Surface-based cortical analyses were performed using Freesurfer 5.0.0 (Fischl and Dale, 2000) (http://surfer.nmr.mgh.harvard.edu). Cortical thickness measures by Freesurfer have been validated against autopsy findings (Rosas et al., 2002) and manual measurements (Salat et al., 2004). Using a surface-based protocol, region-specific atrophy has been shown in various patient populations including small-vessel disease (de Laat et al., 2012), multiple sclerosis (Sailer et al., 2003) and neurodegenerative disease (Dickerson et al., 2009; Du et al., 2007; Rosas et al., 2002).

Surface-based analyses in Freesurfer involved the removal of non-brain tissue using a hybrid watershed algorithm, automated Talairach transformation, segmentation of subcortical white and gray matter, intensity normalization, tessellation of gray/white-matter boundary, automated correction of topological defects, and surface deformation to form the gray and white-matter boundary (Dale et al., 1999). Cortical thickness was determined as the difference between the pial and white-matter surface (Fischl and Dale, 2000).

Cortical segmentations were manually inspected for errors and we used the manual edits as provided in Freesurfer to resolve these errors. Dura was removed manually and control points were used to solve problems in intensity normalization. Lesion filling was used for WMH and LL. In many patients the WMH affected the white–gray matter interface and therefore the border between lesion and white–gray matter interface was not always clear, possibly also due to limitations in the imaging parameters. Lesion filling was therefore in these cases not a solution. Since in many cases the insula and temporal cortex were affected with WMH (Auer et al., 2001; Chabriat et al., 2009), which resulted in cortical segmentation problems, we decided to remove these regions from the analysis in all patients. In the temporal region cortical segmentation was in addition hard because of signal drop-out. For the insula it was hard to reconstruct the white-matter surface since the white-matter adjacent to the claustrum is very thin. The boundaries for these regions were determined by using the Desikan–Killiany parcellation atlas as provided in Freesurfer (Desikan et al., 2006). If extensive errors were observed in one or more areas across the cortex (apart from the removed insula and temporal poles), and these errors could not be resolved, we decided to remove the subject from analysis.

The surface of the gray–white matter border was inflated and smoothed across the surface with a Gaussian smoothing kernel using a full width at half maximum of 10 mm. Single patient data were registered to an average spherical surface representation in Freesurfer (fsaverage), which is an average surface template of 40 subjects, optimally aligning sulcal and gyral features of the brain.