The Effect of Lacunar Infarcts on White Matter Tract Integrity

Yael D. Reijmer, PhD; Whitney M. Freeze, BSc; Alexander Leemans, PhD; Geert Jan Biessels, MD, PhD; on behalf of the Utrecht Vascular Cognitive Impairment Study Group

Background and Purpose—Lacunar infarcts maycause disturbances of the white matter (WM) structure remote from the primary lesion. Here, we used diffusion MRI and tractography to (1) spatially characterize microstructural abnormalities along WM tracts containing a lacunar infarct and (2) relate abnormalities in remote parts of the affected WM tract to cognitive outcome.

Methods—In 17 participants with a lacunar infarct, we reconstructed the affected WM tract using fiber tractography. The corresponding nonlesioned tract in the contralateral hemisphere served as a control tract. Diffusion parameters (fractional anisotropy and mean diffusivity) were plotted along the tract and related to measures of memory, executive functioning and information processing speed.

Results—Diffusion abnormalities remote from the lacune were present in the affected tract compared with the control tract up to 2 cm from the lacune (9% to 17% decrease in fractional anisotropy, 11% to 27% increase in mean diffusivity; P<0.05). The severity of these abnormalities attenuated with increasing distance to the primary lesion. Furthermore, the degree of remote WM disturbances was related to worse cognitive functioning on all 3 domains, independent of the size of the lacune (r=0.6–0.8; P<0.05).

Conclusions—Lacunar infarcts are associated with abnormalities in the affectedWM tract that extend centimeters beyond the lesion visible on conventional MRI. These secondary WM abnormalities may contribute to the cognitive deficits observed in patients with subcortical infarcts. (Stroke. 2013;44:00-00.)

Key Words: brain MRI ■ cognition ■ diffusion tensor imaging ■ lacunar infarct

Lacunar infarcts are generally considered as focal lesions, visible on conventional MRI images. However, it is suggested that ischemic infarcts have more widespread effect on the white matter (WM) microstructure attributable to, for example, secondary degeneration of the affected WM tract or inflammatory responses. The microstructural alterations of the WM can be studied in vivo using diffusion tensor imaging. Recently, it has become possible to spatially characterize WM diffusion abnormalities along the pathway of a specific tract. This method can reveal localized diffusion abnormalities that may not be apparent using an ROI-based or a tract-averaged approach. Until now, however, no study has used this method to examine whether lacunar infarcts are associated with local or more widespread disruptions of the WM structure, and whether these disruptions contribute to worse cognitive outcome. In the present study, we examined the WM microstructure of tracts containing a lacunar infarct and evaluated whether potential WM abnormalities within the affected tract, but remote from the primary lesion, are related to worse cognitive functioning.

Methods
Participants (n=17; age range, 58–87; 57% men) were selected from an ongoing research program on brain MRI markers of vascular cognitive impairment at the University Medical Center Utrecht (for details see Methods in the online-only Data Supplement). To be eligible for the present study, participants should have had a dedicated 3T MRI scan and no diagnosis of dementia or a Mini Mental State Examination <26, or other known neurological disease apart from small vessel disease/noninvalidating stroke. Participants with an infarct in or near the corresponding tract in the contralateral hemisphere, and with a large cortical infarct (>1.5 cm) were excluded. Of the 17 patients, 12 had multiple lacunar infarcts on MRI and 5 of them reported a history of clinical manifest stroke or transient ischemic attack.

MRI data were acquired on a Philips 3.0 Tesla scanner using a standardized protocol, including a diffusion-weighted scan (single-shot spin echo echo planar imaging sequence, 48 contiguous slices, b-value: 1200 s/mm², 1 b=0 s/mm²), a 3-dimensional T1, and a fluid-attenuated inversion recovery scan. Details on the data processing can be found in the Methods in the online-only Data Supplement. Total WM hyperintensity load was assessed on fluid-attenuated inversion recovery scans using a visual rating scale. Cognition was assessed by the Rey Auditory Verbal Learning Test (memory), the Stroop nonverbal test (information processing speed), and by the Trail Making Test A and B (executive functioning).

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From the Department of Neurology, Rudolf Magnus Institute of Neuroscience (Y.D.R., W.M.F., G.J.B.), and Image Sciences Institute (A.L.), University Medical Center Utrecht, The Netherlands.

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Correspondence to Yael Reijmer, PhD, UMC Utrecht, Neurology G03.232, PO Box 85500, 3508GA Utrecht, The Netherlands. E-mail yaelreijmer@gmail.com

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Color-Word Test (information processing speed [card I+II] and executive functioning [card III]), and the Category Verbal Fluency Test (executive functioning).

**Analysis**

For each individual, the fractional anisotropy (FA) and mean diffusivity (MD) of the lesioned tract were expressed as percentage of the control tract: (FAlesioned/FAcontrol)×100%. Thus, we obtained a relative measure of FA and MD for each segment, which is independent of interindividual differences in diffusion tensor imaging metrics related to confounders, such as age and small vessel disease.

The relative FA and MD values of the lesioned tract were compared with the control tract using a Wilcoxon signed-rank test. This was performed for the whole tract, after excluding the segment(s) containing the infarct, and for each individual segment along the tract (Figure 1).

In addition, we related the relative FA/MD of the lesioned tract to cognitive functioning, controlling for age, sex, and level of education. Again, the infarct-containing segment(s) was excluded from the analysis. In secondary models, we adjusted these correlations for the side (left/right) and volume of the lacune and for total WM hyperintensity load.

**Results**

Details on the reconstructed tracts are given in the online-only Data Supplement (Table I in the online-only Data Supplement). Total tract volume did not differ between tracts indicating that tractography was reliably performed in both hemispheres and was not affected by the lacune (Table I in the online-only Data Supplement). Also, total WM hyperintensity load, and the mean FA and MD were not different between the affected and nonaffected hemispheres (P>0.30).

After exclusion of the infarct-containing tract segment(s), diffusion abnormalities were present in the affected tract compared with the control tract, indicated by an overall decrease in FA (93±8%; P=0.002) and an increase in MD (110±13%; P=0.004). Figure 2 shows the relative FA and MD for each segment along the tract. The difference in FA and MD relative to the control tract gradually attenuated with increasing distance to the primary lesion.

A greater decrease in FA in the affected tract relative to the control tract was related to worse executive functioning (Change is Z score per 10% decrease in FA: verbal fluency: −0.85 SD, P=0.024) and information processing speed (Stroop task card I+II: −1.11 SD, P<0.001). A greater increase in MD was also related to slowing of information processing (verbal fluency: −0.49 SD, P=0.033) and to worse memory performance (word-recall task: −0.45 SD, P=0.024). Correlation plots are given in Figure II in the online-only Data Supplement. The correlations remained significant after controlling for the side or the size of the lacune (all P<0.05).

Controlling for total WM hyperintensity load only attenuated the relation between MD and memory (word-recall task: −0.38, P=0.107); all other associations remained significant. Repeating the same analyses in WM tracts in the affected hemisphere not containing a lacune revealed no significant relation between relative FA/MD and cognition (see Results in the online-only Data Supplement).

**Discussion**

This is the first study to assess the impact of a lacunar infarct on the WM structure along a tract using diffusion tensor imaging and tractography. Our results show structural abnormalities remote from the lacune that are not visible on conventional MRI. The severity of the WM abnormalities attenuates with increasing distance to the primary lesion. This pattern suggests that the mechanisms responsible for the degradation in WM structure are directly related to the ischemic lesion. Furthermore, the degree of secondary WM abnormalities were related to worse cognitive functioning independent of the size of the lacune itself.

Potential mechanisms underlying the alterations in diffusion measures include axonal degeneration, demyelination, and chronic inflammatory processes/reactions in the vicinity of small infarcts.1,7 Previous studies in patients with stroke...
have demonstrated WM diffusion abnormalities in the so-called normal appearing WM. Our findings indicate that subcortical infarcts may directly contribute to these diffusion abnormalities by remote effects on the WM structure along affected WM tracts.

Strengths of this study include the comprehensive scan protocol, including high-resolution diffusion MRI data, and the along-tract-based analysis approach. A limitation of this study is the limited sample size, the fact that we were not blinded for the lacune during tract reconstruction, and lack of information on the time since infarction. However, the fact that we focused on cavitating lacunes indicates that all infarcts were examined at a chronic stage. Future longitudinal studies should further examine how secondary WM abnormalities contribute to the cognitive deficits observed in patients with subcortical infarcts.

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Disclosures
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References
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SUPPLEMENTAL MATERIAL

The effect of lacunar infarcts on white matter tract integrity

Yael D. Reijmer PhD¹, Whitney M. Freeze BSc¹, Alexander Leemans PhD², Geert Jan Biessels MD, PhD¹, on behalf of the Utrecht Vascular Cognitive Impairment (VCI) Study Group

¹ Department of Neurology, Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, the Netherlands
² Image Sciences Institute, University Medical Center Utrecht, the Netherlands
Supplemental Methods

Participants

To assess the impact of lacunar infarcts on WM tract structure we applied strict selection criteria, targeting people with a lacunar infarct without other major neurological disease. Participants were selected from an ongoing research program on brain MRI markers of vascular cognitive impairment at the University Medical Center Utrecht\textsuperscript{1, 2} which involves individuals recruited via the memory clinic\textsuperscript{2} or via general practitioners in Utrecht and vicinity\textsuperscript{1}. To be eligible for the present study participants should have had a dedicated 3T MRI scan and no diagnosis of dementia or an MMSE < 26, or another known neurological disease apart from small vessel disease/non-invalidating stroke. From 91 eligible individuals 33 (36\%) had a lacunar infarct on MRI defined as a hypointense lesion < 15mm in diameter on FLAIR and T1 images, with a hyperintense rim on fluid-attenuated inversion recovery (FLAIR) images\textsuperscript{3}. From these 33 individuals with lacunes 21 (64\%) met the following inclusion criteria: a lacunar infarct clearly situated within a WM tract, without an infarct in or near the corresponding tract in the contralateral hemisphere, and without a large cortical infarct (>1.5 cm). These inclusion criteria were verified by at least two raters (Y.R., W.F.). Four subjects had to be excluded because of movement artifacts on the DTI scan, leaving 17 participants for the current analysis (age range: 58-87, 57\% men).

MRI data processing

The diffusion MRI data were corrected for subject motion and eddy current distortions with ExploreDTI (www.exploredti.com) as described previously\textsuperscript{4}. In summary, for each subject, the analysis consisted of the following steps (see Figure 1): (1) the diffusion MRI images were transformed to the T1 images to correct for EPI deformations\textsuperscript{5}; (2) the FLAIR images were registered to the T1 images and used to segment the lacunar infarcts\textsuperscript{6}; (3) fiber tracking was performed based on constrained spherical deconvolution\textsuperscript{7} with parameter settings and region-of-interests (ROIs) as defined previously\textsuperscript{8}; (4) for each white matter tract containing the infarct, the contralateral tract was also reconstructed to serve as the control tract; (5) only the fragment of the tract between the ROIs was analyzed to make sure that the tracts had the same length in both hemispheres; (6) diffusion properties (fractional anisotropy (FA) and mean diffusivity (MD)) were investigated along the tract pathways at 5 mm intervals at both sides of the lesion location\textsuperscript{9}.
FLAIR images were also used to assess white matter hyperintensity (WMH) load using the Age Related White Matter Changes (ARWMC) scale\textsuperscript{10}. This was done by two raters (Y.R., S.H.) who were blinded for clinical data. Total WMH load was defined as the sum score of all brain regions per hemisphere (range 0-15).

**Results**

**Additional analyses**

To verify whether the described correlations with cognition are specific to the lesioned tract and not due to more diffuse properties of the lacune-containing hemisphere we reconstructed a second tract from affected hemisphere, but this time without a lacune. We again expressed the FA/MD of this tract relative to the FA/MD of the same tract in the contra-lateral hemisphere. We selected the same type of tracts as in Table S1, including the uncinate fasciculus, the inferior fronto-occipital fasciculus, the corticospinal tract, the inferior longitudinal fasciculus, the splenium of the corpus callosum and the tapetum. There was no difference in relative FA or MD between the control tracts from the affected and non-affected hemisphere (mean±SD relative FA: 99 ± 10%; MD 101 ± 4%; \( p > 0.332 \)). Also, no relation was found between the relative FA/MD of the control tract in the affected hemisphere and cognitive functioning (Table S2).
Supplemental Tables

Table S1. Participant characteristics and affected WM tracts

<table>
<thead>
<tr>
<th>Subject nr</th>
<th>Age (years)</th>
<th>sex</th>
<th>Total nr of lacunes</th>
<th>Reconstructed tract</th>
<th>Hemisphere affected tract</th>
<th>Tract volume (mm^3) with lesion</th>
<th>Tract volume (mm^3) contra-lateral hemisphere</th>
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<td>1567</td>
<td>1709</td>
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</table>

a Five of these patients (nr. 2, 5, 12, 15, 16) reported a history of clinical manifest stroke, 2 months-8 years prior to scanning

b The estimated tract volume did not differ between the affected and control tract (p>0.05)

M=male, F=female, R=right, L=left
Table S2. Relation between FA/MD of WM tracts in the affected hemisphere, but not containing a lacune and cognition

<table>
<thead>
<tr>
<th></th>
<th>Relative FA control tract %</th>
<th>Relative MD control tract %</th>
</tr>
</thead>
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<tr>
<td>Verbal fluency task</td>
<td>-0.057 (0.846)</td>
<td>0.126 (0.667)</td>
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<tr>
<td>Word recall task</td>
<td>-0.174 (0.551)</td>
<td>0.032 (0.913)</td>
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<td>Stroop task, mean card I+II</td>
<td>-0.027 (0.930)</td>
<td>0.187 (0.540)</td>
</tr>
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</table>

Partial correlation coefficients (p-value). FA and MD are expressed as percentage relative to the tract in the contralateral hemisphere. Correlations were corrected for age, sex, and education level.

Supplemental Figure

Figure S1. Correlation between relative FA (top row) and MD (bottom row) of the affected tract and cognitive functioning. The segment(s) containing the lacune is excluded from the analysis. FA and MD are expressed as percentage relative to the control tract. Cognitive tests scores are presented as z-scores adjusted for age, sex, and education level.
References


