Acute infarcts cause focal thinning in remote cortex via degeneration of connecting fiber tracts

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ABSTRACT

Objective: To study remote effects distant from acute ischemic infarcts by measuring longitudinal changes of cortical thickness in connected brain regions as well as changes in microstructural integrity in connecting fiber tracts.

Methods: Thirty-two patients (mean age 71 years) underwent a standardized protocol including multimodal MRI and clinical assessment both at stroke onset and 6 months after the event. Cortex connected to acute infarcts was identified by probabilistic diffusion tensor tractography starting from the acute lesion. Changes of cortical thickness were measured using the longitudinal stream of FreeSurfer. Microstructural damage in white matter tracts was assessed by changes of mean diffusivity.

Results: We found focal cortical thinning specifically in areas connected to acute infarcts ($p < 0.001$). Thinning was more pronounced in regions showing a high probability of connectivity to infarcts. Microstructural damage in white matter tracts connecting acute infarcts with distant cortex significantly correlated with thickness changes in that region ($\rho = -0.39$, $p = 0.028$). There was no indication of an influence of cavitation status or infarct etiology on the observed changes in cortex and white matter.

Conclusions: These findings identify secondary degeneration of connected white matter tracts and remote cortex as key features of acute ischemic infarcts. Our observations may have implications for the understanding of structural and functional reorganization after stroke.
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GLOSSARY

FLAIR = fluid-attenuated inversion recovery; **MD** = mean diffusivity; **ROI** = region of interest.

Remote cortical effects of acute infarcts critically contribute to functional reorganization after stroke and influence clinical outcome.[1,2] We recently identified focal cortical thinning as a potential structural correlate of remote effects after ischemic lesions. In a small retrospective study on 9 patients with inherited small vessel disease, we showed that incident subcortical lacunes are associated with focal thinning in cortex connected to the infarct.[3,4] We attributed these findings to secondary cortical neurodegeneration following damage to the connecting subcortical fiber tracts. However, the study protocol and small sample size precluded a detailed assessment of these tracts and how changes in these tracts relate to changes in the connected cortex. Also, the results were obtained in a rare hereditary condition and were limited to a single infarct mechanism and to chronic, cavitating infarcts.

In the current prospective, longitudinal study, we investigated the processes driving secondary neurodegeneration after acute infarcts. We measured changes of cortical thickness and microstructural integrity of connecting white matter tracts over a 6-month interval starting from stroke onset. We tested the following hypotheses: (1) cortical thinning in connected cortical regions is detectable within a few months after an acute infarct; (2) cortical thinning relates to

Supplemental data at Neurology.org

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structural alterations in the connecting fiber tract; (3) acute infarcts turning into cavitating lesions (i.e., more severe tissue injury) show more pronounced cortical thinning compared with noncavitating infarcts; and (4) secondary cortical thinning is a general phenomenon not restricted to specific infarct etiologies.

Table 1 Characteristics of the study cohort

	Study cohort (n = 32)
Demographics	
Age, y, mean (SD), range	70.9 (7.23), 55–83
Male, n (%)	23 (72)
Infarct volumes on baseline DWI, mm³, median (IQR)	
All infarcts	356 (2,762)
Infarcts with cavitation on follow-up scan (n = 19)	448 (4,656)
Infarcts without cavitation on follow-up scan (n = 10)	424 (594)
Infarcts with no visible lesion on follow-up scan (n = 3)	208 (20)
Stroke etiology (TOAST classification[38]), n (%)	
Large artery atherosclerosis, extracranial	3 (9.4)
Large artery atherosclerosis, intracranial	3 (9.4)
Cardioembolism	5 (15.6)
Small vessel occlusion	7 (21.9)
Stroke of other determined etiology	1 (3.1)
Stroke of undetermined etiology, 2 or more causes	2 (6.2)
Stroke of undetermined etiology, negative evaluation	11 (34.4)
Vascular risk factors, n (%)	
Hypertension	17 (53.1)
Hypercholesterolemia	11 (34.4)
Diabetes	5 (15.6)
Smoking[a]	16 (50.0)
Clinical scores, median (IQR)	
Modified Rankin Scale, before stroke	0 (0)
Modified Rankin Scale, baseline	1 (1.25)
Modified Rankin Scale, follow-up	0 (1)
NIHSS, baseline	2 (4)
NIHSS, follow-up	0 (2)
Cognitive scores, median (IQR)	
MOCA, baseline	26.5 (5.0)
MOCA, follow-up	26.0 (3.5)
MMSE, baseline	29.0 (3.5)
MMSE, follow-up	29.0 (2.0)
Other imaging characteristics	
Normalized WMH volume, %, median (IQR)	0.28 (0.27)
Presence of lacune at baseline, n (%)	1 (3.1)

Abbreviations: DWI = diffusion-weighted imaging; IQR = interquartile range; MMSE = Mini-Mental State Examination; MOCA = Montreal Cognitive Assessment; NIHSS = NIH Stroke Scale; TOAST = Trial of Org 10172 in Acute Stroke Treatment; WMH = white matter hyperintensities.
[a] Past or current smoking, 6 months or longer.

METHODS Study cohort. Patients with a first-ever acute ischemic stroke were recruited between February 2012 and May 2013 through the ongoing prospective observational DEDEMAS (Determinants of Dementia After Stroke, NCT01334749) study.[5] The final sample (e-Methods on the *Neurology*® Web site at Neurology.org) comprised 32 patients (tables 1 and e-1). We used data from the acute phase (baseline) and from follow-up 6 months after stroke.

Standard protocol approvals, registrations, and patient consents. All procedures were approved by the local ethics committee and written informed consent was obtained from each patient.

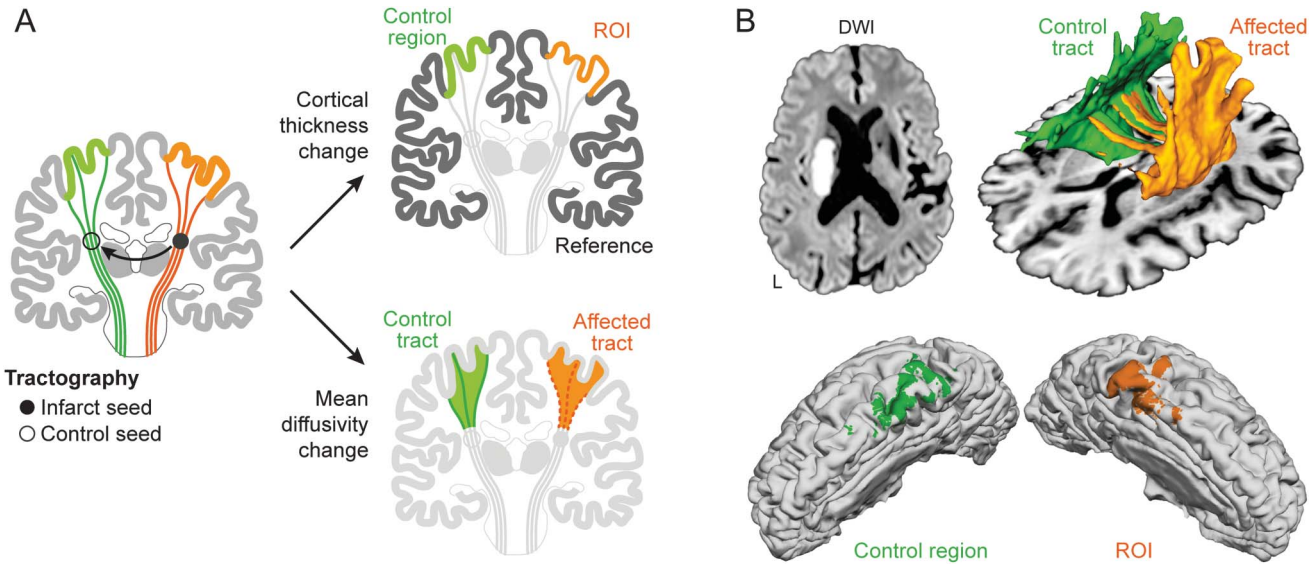
MRI acquisition. Data were acquired on a single 3T MRI scanner (Siemens Magnetom Verio) using a 32-channel head coil (Siemens Medical Systems, Erlangen, Germany). Baseline and follow-up scans were obtained using the identical standardized imaging protocol (e-Methods).

Infarct segmentation and identification of connected cortex. Acute infarcts (subcortical and cortical) were manually segmented on baseline diffusion-weighted images taking the hyperintense area corresponding to the acute cytotoxic edema.[6] The segmentation masks were used as seed for probabilistic tractography (e-Methods) to identify the cortical area connected with the infarct. This area was defined as the cortical region of interest (ROI) (figure 1A). Control regions were determined by the identical procedure but using a tractography seed manually placed at the corresponding location in the contralateral hemisphere. All tractographic results were checked visually for plausibility while ensuring that tracts from the infarct seed were largely similar to those obtained from the control seed in the contralateral hemisphere (figure 1B). Probabilistic tractography was performed at different levels for the probability of connectivity. Lower levels are more susceptible to noise and may lead to false-positive tracts while higher levels are more specific but might eliminate subordinate pathways. For details, see e-Methods.

Cortical thickness measurements. Surface-based cortical analyses were performed using FreeSurfer, version 5.1.0.[7,8] Cortical thickness measures by FreeSurfer have been validated against autopsy findings[9] and manual measurements,[10] and allow measurements of cortical thickness in the submillimeter scale.[8] To extract reliable estimates for the change in cortical thickness between baseline and follow-up scans, images were automatically processed through the longitudinal stream.[11] The procedure is optimized for longitudinal data using an unbiased within-subject template space and image.[12] Processing steps are initialized with common information from this template. The longitudinal stream offers significantly increased statistical power compared with cross-sectional processing.[11] Cortical segmentations were carefully inspected. In cases where cortex was incorrectly segmented (mostly due to reduced gray–white contrast) and could not be corrected after reprocessing, we removed the respective area from the analysis. This was only the case for 5 patients and the removed surface did not exceed 1.03% of the total surface area. Cortical regions directly affected by the infarct were excluded from the thickness measurements.

We assessed the change in cortical thickness in the ROI (corresponding to the infarct seed) or control region (control seed). Cortex outside the ROI and outside the control region was

Figure 1 Illustration of the study design



(A) Tractography was performed for the infarct seed and the control seed (corresponding location in the contralateral hemisphere) to identify the connected cortical ROI (orange band), the control region (green band), and connecting fiber tracts. Changes in cortical thickness over time were measured using the remaining cortex (dark gray) as a reference. Changes of microstructural integrity of connecting fiber tracts were determined by measuring mean diffusivity. (B) Representative example of a patient with an acute stroke: DWI shows a lesion in the left hemisphere corresponding to an acute striatocapsular infarct. Tracts from probabilistic tractography for the infarct seed (orange) and the control seed (green) are shown as 3-dimensional volume renderings and appear largely similar. Tracking of crossing fibers can be observed at the corpus callosum. The resulting cortical regions are depicted on a 3-dimensional model of the pial surface. DWI = diffusion-weighted imaging; ROI = region of interest.

defined as reference region and used to correct for global thickness changes: we defined the "change in focal cortical thickness" as the change of thickness exceeding the change in the reference region. We thereby corrected for global changes in cortical thickness unrelated to the infarct, such as hydration status of the patient,[13] or comorbid pathologies affecting cortical thickness, e.g., Alzheimer disease.

Analysis of tract mean diffusivity. Microstructural alterations in connecting fiber tracts were analyzed by measuring mean diffusivity (MD). MD is a sensitive and robust measure of microstructural white matter alterations after stroke[14,15] and is preferred over other diffusion tensor imaging measures because it is less affected by the directionality of different tracts.

Mean MD values were obtained for the affected tract (originating from the infarct) and the control tract (originating from the control seed) both at baseline and at follow-up and changes in MD over time were calculated. For details, see e-Methods.

Infarct status at follow-up. Infarcts identified on diffusion-weighted images can have different appearances on follow-up imaging, ranging from cavitation (complete tissue loss) to normal-appearing.[16–18] To assess the relationship between different imaging appearances on follow-up examinations and changes within the connected cortex or the affected tracts, infarcts were classified into 3 groups using the T1-weighted and fluid-attenuated inversion recovery (FLAIR) images at follow-up: (1) cavitating (parts of the infarct turned into a cavity), (2) noncavitating (no cavitation, parts of the infarct turned into a FLAIR hyperintensity), and (3) no visible T1 or FLAIR lesion at the site of the original infarct.

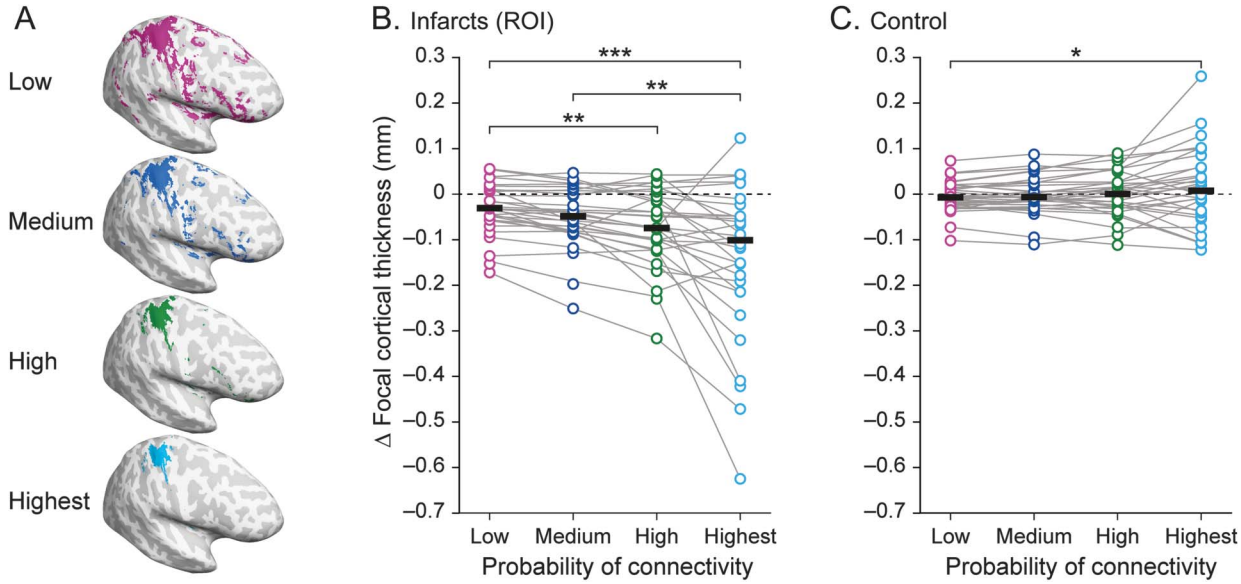
Statistical analyses. The Shapiro-Wilk test showed that several variables deviated from normal distribution. Therefore, nonparametric tests were used throughout to ensure robustness of the statistical analyses (R software package, version 2.13.2; R Foundation for Statistical Computing, Vienna, Austria). For details, see e-Methods.

RESULTS

Characteristics of the study cohort. Demographic and clinical characteristics of the study cohort, as well as infarct characteristics are provided in table 1. On average, patients were relatively mildly affected as reflected by the NIH Stroke Scale score, the modified Rankin Scale score, and cognitive scores. Stroke etiologies varied with a high proportion of cryptogenic strokes despite extensive diagnostic workup. The mean interval between symptom onset and baseline MRI was 84.4 hours (SD = 38.2). The mean interval between baseline and follow-up examinations was 6.07 months (SD = 0.66, range = 4.0–7.5). No patient had a recurrent infarct during the follow-up period as judged by clinical information and MRI.

Focal cortical thinning in areas connected to the infarct. We first measured the change of focal cortical thickness between baseline and follow-up in cortical areas connected to the infarct (ROI; figures 1 and 2B). There was a statistically significant decrease in focal cortical thickness at all connectivity levels studied (low: $V = 418$, $p = 0.0032$; medium: $V = 468$, $p < 0.001$; high: $V = 474$, $p < 0.001$; highest: $V = 491$, $p < 0.001$; 2-tailed Wilcoxon signed rank test) (figure 2B). Analyses across connectivity levels

Figure 2 Focal cortical thickness changes in connected ROI and control region



(A) Example images of cortical ROIs at different probabilities of connectivity with the acute infarct. Cortical ROIs of a single individual are shown on the inflated pial surface (light gray depicts cortex on gyri, dark gray in sulci). (B, C) Changes in focal cortical thickness in the ROI (cortex connected to the infarct, B) and the control region (connected to the control seed, C) at 4 connectivity levels. Each line represents one patient. Black bars depict the group median. $*p < 0.05$, $**p < 0.01$, and $***p < 0.001$ (nonparametric post hoc test). ROI = region of interest.

showed more pronounced focal cortical thinning with higher probability of connectivity ($\chi^2 = 27.60$, $df = 3$, $p < 0.001$; Friedman rank sum test). At the highest level (1,000mm^2 surface area), 27 of 32 patients showed focal cortical thinning in the ROI.

Using control seeds from the contralateral side, we found no change of focal cortical thickness at any connectivity level in the control region (low: V = 321, $p = 0.295$; medium: V = 308, $p = 0.421$; high: V = 275, $p = 0.847$; highest: V = 234, $p = 0.586$) (figure 2C), while analyses across connectivity levels showed a weak main effect ($\chi^2 = 9.08$, $df = 2$, $p = 0.028$).

A similar pattern of focal cortical thinning in the ROI showing increasing magnitude with higher connectivity was found in all etiologic subgroups (figure e-1), although the low number of subjects within subgroups precluded a meaningful statistical analysis.

Decline of microstructural integrity in connecting fiber tracts. We next assessed the effect of acute infarcts on the integrity of fiber tracts connecting the infarct with the cortex. MD values at baseline were not significantly different between the affected tract and the control tract in the contralateral hemisphere (V = 307, $p = 0.427$) (figure 3A). MD values increased from baseline to follow-up both in the affected (V = 525, $p < 0.001$) and in the control tracts (V = 435, $p < 0.001$). However, MD values at follow-up were significantly higher in the affected compared with the control tracts (V = 446, $p < 0.001$). Also, the increase in MD between baseline and follow-up was greater in affected compared with control tracts (V = 492, $p < 0.001$).

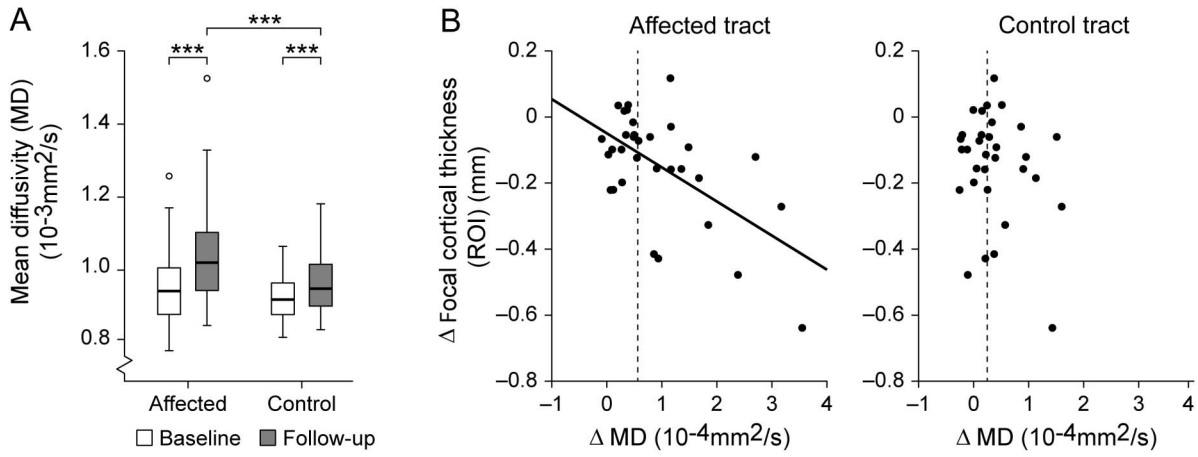
Focal cortical thinning relates to decline in fiber tract integrity. To explore the relationship between alterations in connecting fiber tracts and connected cortical regions, we next correlated longitudinal changes in diffusion tensor imaging metrics and cortical thickness. Changes in MD in affected fiber tracts significantly correlated with changes of cortical thickness in connected brain areas. Increases of MD were associated with focal cortical thinning in ROIs ($\rho = -0.39$, S = 3,330, $p = 0.028$; Spearman rank correlation) whereas there was no correlation between the change of MD in the control tracts and the change of cortical thickness within ROIs ($\rho = -0.10$, S = 4,924, $p = 0.595$) (figure 3B).

Infarct characteristics and cortical thinning. Infarct volume was significantly correlated with focal cortical thinning in the ROI ($\rho = 0.51$, S = 2,680, $p = 0.030$) as well as the MD change in the affected tract ($\rho = 0.60$, S = 2,170, $p < 0.001$).

In 19 patients (59%), infarcts showed at least some cavitation on follow-up scans (cavitating infarct). In 10 patients (31%), the infarct turned into a lesion hyperintense on FLAIR images but without cavitation (noncavitating infarct), and in 3 patients (9%), there was no visible lesion on T1-weighted and FLAIR images at follow-up.

There was no significant difference between patients with cavitating or noncavitating infarcts regarding cortical thinning in the ROI at any connectivity level (figure 4;

Figure 3 MD in affected tracts relates to focal cortical thinning

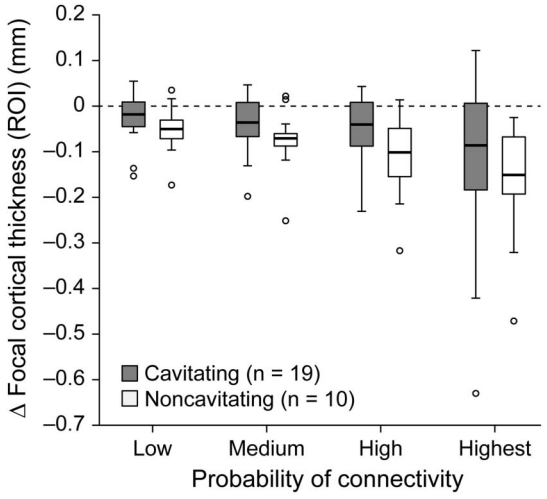


(A) Boxplots for the MD in affected and control tracts at baseline and follow-up. ***$p < 0.001$ (2-tailed Wilcoxon signed rank test). (B) Scatterplots for the change in cortical thickness in the ROI vs the change in MD. Results are shown both for the affected tract and the control tract. A significant relationship was found for the MD change in the affected tract but not for the control tract. The dashed line indicates the group median for the change in MD. MD = mean diffusivity; ROI = region of interest.

low: W = 130, $p = 0.115$; medium: W = 130, $p = 0.115$; high: W = 128, $p = 0.138$; highest: W = 118, $p = 0.308$). In addition, there was no difference in the change of MD in the affected tract (W = 90, $p = 0.839$) between cavitating and noncavitating infarcts.

Of note, patients with no visible lesion on follow-up scans (n = 3) showed a considerable degree of focal cortical thinning in the ROI (−0.054 mm, −0.108 mm, and −0.214 mm at the highest probability of connectivity) comparable to the amount of focal thickness change in the overall group (interquartile range: −0.048 to −0.197 mm).

Figure 4 Influence of infarct cavitation



Relationship between the cavitation status of the infarct at follow-up and the change of focal cortical thickness in the ROI. Boxplots are shown for the group of patients with cavitating and noncavitating infarcts. There was no significant difference at any of the 4 connectivity levels. Infarcts resolving without a visible lesion at follow-up (n = 3) are not included. ROI = region of interest.

DISCUSSION In the current study, we investigated remote secondary effects of acute infarcts on connected cortex and connecting fiber tracts. Our main findings can be summarized as follows: (1) acute infarcts induced focal degenerative changes in cortical regions connected to the infarct; (2) this was paralleled by a degeneration of connecting fiber tracts; (3) the degree of cortical thinning correlated with the loss of microstructural integrity in connecting white matter tracts; and (4) remote effects were seen regardless of the fate of the acute infarct, i.e., whether the infarct turned into a cavitating or noncavitating lesion. These findings highlight secondary neurodegeneration as an important feature of brain infarcts and may have implications for the understanding of structural and functional reorganization after stroke.

The presence of focal gray matter atrophy together with loss of microstructural integrity in connecting fiber tracts is strongly indicative of neurodegeneration. Acute cortical infarcts in the middle cerebral artery territory have been shown to induce a delayed and selective reduction of neuronal density in the ipsilateral thalamus[19] and substantia nigra,[20] both in humans and in experimental models.[21] These pathologic findings are complemented by human imaging studies demonstrating remote changes in the thalamus and substantia nigra after stroke.[22–26] Of note, however, these studies did not investigate the connecting fiber tracts and mostly focused on deep gray matter. A mechanism of secondary neurodegeneration is further supported by the observation that infarcts affecting the motor cortex or descending pathways may cause wallerian degeneration of the distal corticospinal tract, which continues over several weeks.[27] Secondary neurodegeneration after infarction may even

extend beyond synapses. Retinal measurements in patients with damage to postgeniculate visual pathways revealed thinning of the retinal nerve fiber layer that extended over many months.[28] Thus, it might be that the decline of cortical thickness detected in the current study in part reflects transsynaptic effects on cortical neurons, such as shrinkage of dendrites and cell bodies due to loss of synaptic input.[29]

By taking the acute infarct as a tractography seed, we were able to study a precisely defined time window starting with the initial injury. We are not aware of any similar studies that have followed the degeneration of fiber tracts and cortical morphology right from infarct onset. In fact, most previous studies that addressed secondary neurodegeneration after stroke were cross-sectional and included patients at variable time intervals after stroke, some of them using autopsy material. In the current study, the degree of thinning measured 6 months after the acute injury was quite variable. In contrast, thickness measures in the contralateral control region remained largely stable. The degree of microstructural injury within fiber tracts connected to the infarcts also varied as expressed by variable increases in MD values over time. It is of interest that MD values also increased in the control tracts, albeit to a far lesser extent. We can only speculate on the structural correlates of this increase. However, one possible explanation might be degenerative processes involving crossing fibers.

Of note, regional thickness changes of cortex connected to the infarct correlated with changes of MD in connecting fiber tracts whereas there was no correlation with changes of MD in the control tracts. Considering that the connecting fiber tracts represented the anatomical link between cortex and the acute infarct, it seems justified to conclude that the degenerative changes within cortex were in fact mediated by degeneration of the connecting fiber tracts.

When analyzing the degree of tissue injury we found that the amount of thinning induced by noncavitating infarcts was comparable to that induced by cavitating infarcts, which represent complete tissue loss and therefore more severe injury. This was unexpected and may in fact offer interesting insights. The observation that noncavitating infarcts induced a similar degree of cortical thinning might indicate that acute ischemic injury, even if less severe, is already sufficient to trigger a long-lasting response in remote brain regions. This interpretation is further supported by the observation that cortical thinning was also seen with infarcts that resolved without a visible lesion on follow-up scans. Notably, our observations agree with studies on traumatic brain injury showing that even minor brain injury can trigger degeneration of both gray and white matter.[30,31]

Cortical atrophy has been identified as a strong predictor of poor functional outcome after stroke.[32] The amount of thinning observed in our patients (approximately 2%–5% in 6 months) is beyond reported atrophy rates for community-dwelling elderly[33] and comparable to the thickness decline in patients with Alzheimer disease.[34] In the current study, we found no association between remote changes in cortex or connecting fiber tracts and clinical outcome (supplementary results, table e-2). This might relate to several factors. First, our sample was relatively small and thus probably underpowered. Second, patients were rather mildly affected, which limited our ability to detect clinico-radiologic correlations, and our assessment instruments may not have been sufficiently sensitive. Third, infarct characteristics such as location, volume, and severity of tissue damage largely varied. These factors are all known to influence the clinical expression and severity of symptoms.[35,36]

Our study demonstrates the feasibility of tractography using acute infarcts as a starting point. The validity of the tractographic results is illustrated by the good agreement with measurements from the contralateral noninfarcted hemisphere starting with a seed that corresponded to the location of the diffusion-weighted imaging lesion (figure 1). Our study further shows that this approach can successfully be applied to identify connected cortex already in the acute phase of stroke. The method has implications for future applications. Aside from mechanistic studies on ischemia-induced neurodegeneration, the approach could be used to explore structure-function relationships including aspects of recovery after stroke.[1] Infarct-guided tractography could further be utilized to target cortical regions for focused interventions such as transcranial magnetic stimulation.[1,37]

A limitation of this study is the relatively low number of subjects within subgroups, precluding meaningful analyses on the influence of infarct location or differences between etiologic subgroups. Second, our patients might not be fully representative of a typical stroke sample in that they were relatively mildly affected. Third, analyses were limited to 2 time points and we provide no direct proof that the observed cortical changes were in fact mediated by the observed degeneration of connecting white matter tracts. However, we find it difficult to think of alternative explanations of our data. Finally, and for similar reasons, we can make no inferences on the dynamics of secondary neurodegeneration including whether degeneration continues beyond the time window under study.

Specific strengths of this study include the prospective longitudinal design, the well-characterized patient sample, and a dedicated protocol for

combining tractography with structural measurements of gray and white matter. Also, cortical data were processed using a protocol optimized for longitudinal studies (FreeSurfer longitudinal stream), thus allowing the detection of thickness changes in the submillimeter range.

Our data provide direct evidence in humans that acute infarcts induce focal cortical thinning in remote brain regions via connecting fiber tracts. The findings highlight secondary neurodegeneration within affected tracts and connected cortex as an important feature of brain infarcts and may have implications for the understanding of structural and functional reorganization after stroke.

AUTHOR CONTRIBUTIONS

Dr. Duering: study concept and design, interpretation of data, drafting the manuscript. Dr. Righart: study design, data analysis, statistical analysis, drafting the manuscript. Dr. Wollenweber: data collection, revising the manuscript. Dr. Zietemann: data analysis, revising the manuscript. Dr. Gesierich: data analysis, revising the manuscript. Dr. Dichgans: study concept and design, study supervision, revising the manuscript.

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DISCLOSURE

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REFERENCES

1. Grefkes C, Fink GR. Connectivity-based approaches in stroke and recovery of function. Lancet Neurol 2014;13:206–216.
2. Grefkes C, Nowak DA, Eickhoff SB, et al. Cortical connectivity after subcortical stroke assessed with functional magnetic resonance imaging. Ann Neurol 2008;63:236–246.
3. Duering M, Righart R, Csanadi E, et al. Incident subcortical infarcts induce focal thinning in connected cortical regions. Neurology 2012;79:2025–2028.
4. Smith EE, Arboix A. Focal cortical thinning is caused by remote subcortical infarcts: spooky action at a distance. Neurology 2012;79:2016–2017.
5. Wollenweber FA, Zietemann V, Rominger A, et al. The Determinants of Dementia After Stroke (DEDEMAS) Study: protocol and pilot data. Int J Stroke 2014;9:387–392.
6. Merino JG, Warach S. Imaging of acute stroke. Nat Rev Neurol 2010;6:560–571.
7. Fischl B. FreeSurfer. Neuroimage 2012;62:774–781.
8. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci USA 2000;97:11050–11055.
9. Rosas HD, Liu AK, Hersch S, et al. Regional and progressive thinning of the cortical ribbon in Huntington's disease. Neurology 2002;58:695–701.
10. Salat DH, Buckner RL, Snyder AZ, et al. Thinning of the cerebral cortex in aging. Cereb Cortex 2004;14:721–730.
11. Reuter M, Schmansky NJ, Rosas HD, Fischl B. Within-subject template estimation for unbiased longitudinal image analysis. Neuroimage 2012;61:1402–1418.
12. Reuter M, Fischl B. Avoiding asymmetry-induced bias in longitudinal image processing. Neuroimage 2011;57:19–21.
13. Streitburger DP, Moller HE, Tittgemeyer M, Hund-Georgiadis M, Schroeter ML, Mueller K. Investigating structural brain changes of dehydration using voxel-based morphometry. PLoS One 2012;7:e44195.
14. Kuceyeski A, Kamel H, Navi BB, Raj A, Iadecola C. Predicting future brain tissue loss from white matter connectivity disruption in ischemic stroke. Stroke 2014;45:717–722.
15. Reijmer YD, Freeze WM, Leemans A, Biessels GJ; Utrecht Vascular Cognitive Impairment Study Group. The effect of lacunar infarcts on white matter tract integrity. Stroke 2013;44:2019–2021.
16. Moreau F, Patel S, Lauzon ML, et al. Cavitation after acute symptomatic lacunar stroke depends on time, location, and MRI sequence. Stroke 2012;43:1837–1842.
17. Potter GM, Doubal FN, Jackson CA, et al. Counting cavitating lacunes underestimates the burden of lacunar infarction. Stroke 2010;41:267–272.
18. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 2013;12:822–838.
19. Ogawa T, Yoshida Y, Okudera T, Noguchi K, Kado H, Uemura K. Secondary thalamic degeneration after cerebral infarction in the middle cerebral artery distribution: evaluation with MR imaging. Radiology 1997;204:255–262.
20. Forno LS. Reaction of the substantia nigra to massive basal ganglia infarction. Acta Neuropathol 1983;62:96–102.
21. Baron JC, Yamauchi H, Fujioka M, Endres M. Selective neuronal loss in ischemic stroke and cerebrovascular disease. J Cereb Blood Flow Metab 2014;34:2–18.
22. Tamura A, Tahira Y, Nagashima H, et al. Thalamic atrophy following cerebral infarction in the territory of the middle cerebral artery. Stroke 1991;22:615–618.
23. Herve D, Molko N, Pappata S, et al. Longitudinal thalamic diffusion changes after middle cerebral artery infarcts. J Neurol Neurosurg Psychiatry 2005;76:200–205.
24. Ogawa T, Okudera T, Inugami A, et al. Degeneration of the ipsilateral substantia nigra after striatal infarction: evaluation with MR imaging. Radiology 1997;204:847–851.
25. Nakane M, Teraoka A, Asato R, Tamura A. Degeneration of the ipsilateral substantia nigra following cerebral infarction in the striatum. Stroke 1992;23:328–332.

26. Brodtmann A, Pardoe H, Li Q, Lichter R, Ostergaard L, Cumming T. Changes in regional brain volume three months after stroke. J Neurol Sci 2012;322:122–128.
27. Buss A, Pech K, Merkler D, et al. Sequential loss of myelin proteins during Wallerian degeneration in the human spinal cord. Brain 2005;128:356–364.
28. Jindahra P, Petrie A, Plant GT. The time course of retrograde trans-synaptic degeneration following occipital lobe damage in humans. Brain 2012;135:534–541.
29. Siffrin V, Vogt J, Radbruch H, Nitsch R, Zipp F. Multiple sclerosis: candidate mechanisms underlying CNS atrophy. Trends Neurosci 2010;33:202–210.
30. Johnson VE, Stewart JE, Begbie FD, Trojanowski JQ, Smith DH, Stewart W. Inflammation and white matter degeneration persist for years after a single traumatic brain injury. Brain 2013;136:28–42.
31. Bigler ED. Traumatic brain injury, neuroimaging, and neurodegeneration. Front Hum Neurosci 2013;7:395.
32. Mok V, Xiong Y, Wong KK, et al. Predictors for cognitive decline in patients with confluent white matter hyperintensities. Alzheimers Dement 2012;8:S96–S103.
33. Jiang J, Sachdev P, Lipnicki DM, et al. A longitudinal study of brain atrophy over two years in community-dwelling older individuals. Neuroimage 2014;86:203–211.
34. Clarkson MJ, Cardoso MJ, Ridgway GR, et al. A comparison of voxel and surface based cortical thickness estimation methods. Neuroimage 2011;57:856–865.
35. Duering M, Gesierich B, Seiler S, et al. Strategic white matter tracts for processing speed deficits in age-related small vessel disease. Neurology 2014;82:1946–1950.
36. Duering M, Zieren N, Herve D, et al. Strategic role of frontal white matter tracts in vascular cognitive impairment: a voxel-based lesion-symptom mapping study in CADASIL. Brain 2011;134:2366–2375.
37. Zhang J, Zhang Y, Xing S, Liang Z, Zeng J. Secondary neurodegeneration in remote regions after focal cerebral infarction: a new target for stroke management? Stroke 2012;43:1700–1705.
38. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35–41.