Strategic white matter tracts for processing speed deficits in age-related small vessel disease

Marco Duering, MD*
 Benno Gesierich, PhD*
 Stephan Seiler, MD
 Lukas Pirpamer
 Mariya Gonik, PhD
 Edith Hofer, PhD
 Eric Jouvent, MD, PhD
 Edouard Duchesnay, PhD
 Hugues Chabriat, MD,
 PhD
 Stefan Ropele, PhD
 Reinhold Schmidt, MD
 Martin Dichgans, MD

Correspondence to
 Dr. Dichgans:
martin.dichgans@med.uni-muenchen.de

ABSTRACT

Objective: Cerebral small vessel disease is the most common cause of vascular cognitive impairment and typically manifests with slowed processing speed. We investigated the impact of lesion location on processing speed in age-related small vessel disease.

Methods: A total of 584 community-dwelling elderly underwent brain MRI followed by segmentation of white matter hyperintensities. Processing speed was determined by the timed measure of the Trail Making Test part B. The impact of the location of white matter hyperintensities was assessed by voxel-based lesion-symptom mapping and graph-based statistical models on regional lesion volumes in major white matter tracts.

Results: Voxel-based lesion-symptom mapping identified multiple voxel clusters where the presence of white matter hyperintensities was associated with slower performance on the Trail Making Test part B. Clusters were located bilaterally in the forceps minor and anterior thalamic radiation. Region of interest-based Bayesian network analyses on lesion volumes within major white matter tracts depicted the same tracts as direct predictors for an impaired Trail Making Test part B performance.

Conclusions: Our findings highlight damage to frontal interhemispheric and thalamic projection fiber tracts harboring frontal-subcortical neuronal circuits as a predictor for processing speed performance in age-related small vessel disease. *Neurology*® 2014;82:1946-1950

GLOSSARY

ASPFS = Austrian Stroke Prevention Family Study; **ASPS** = Austrian Stroke Prevention Study; **ATR** = anterior thalamic radiation; **Fmin** = forceps minor; **SVD** = small vessel disease; **TMT-B** = Trail Making Test, matrix B; **VCI** = vascular cognitive impairment; **VLSM** = voxel-based lesion-symptom mapping; **WMH** = white matter hyperintensities.

Deficits in processing speed are among the earliest and most prominent cognitive manifestations of cerebral small vessel disease (SVD). By studying patients with an inherited variant of early-onset SVD, we recently demonstrated a strategic role of SVD-related lesions¹ within frontal-subcortical neuronal circuits in determining impaired processing speed.^{2,3} However, the generalizability of these findings to sporadic SVD in the elderly general population remains unexplored.

In the current study, we examined 584 healthy subjects from a community-dwelling cohort collected through the Austrian Stroke Prevention Study (ASPS). We focused on white matter hyperintensities (WMH) as the most common neuroimaging manifestation and on processing speed as the most prominently affected cognitive domain in SVD. Relationships between WMH and processing speed as determined by the Trail Making Test, matrix B (TMT-B) were investigated at the level of voxels, using voxel-based lesion-symptom mapping (VLSM), and at the level of regional lesion volumes within major white matter tracts, using Bayesian network analysis. We hypothesized that deficits in processing speed would be related to lesions at strategic locations.

METHODS Study subjects and neuropsychology. We included 601 community-dwelling, clinically healthy subjects with neuroimaging data from the ASPS and the Austrian Stroke Prevention Family Study (ASPFS) (Department of Neurology, Medical

*These authors contributed equally to this work.

From the Institute for Stroke and Dementia Research (M. Duering, B.G., M.G., M. Dichgans), Klinikum der Universität München, Munich, Germany; the Department of Neurology (S.S., L.P., E.H., S.R., R.S.), Medical University of Graz; the Institute for Medical Informatics, Statistics and Documentation (E.H.), Graz, Austria; the Department of Neurology (E.J., H.C.), CHU Lariboisière, Assistance Publique des Hôpitaux de Paris; Neurospin (E.D.), CEA Saclay, Gif sur Yvette, France; the German Center for Neurodegenerative Diseases (DZNE, Munich) (M. Dichgans); and Munich Cluster for Systems Neurology (SyNergy) (M. Dichgans), Munich, Germany.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Editorial, page 1940

Supplemental data
 at Neurology.org

University of Graz).⁴ Seventeen subjects (2.8%) had to be excluded based on incidental MRI findings, technical reasons, or missing cognitive data (see e-Methods on the *Neurology*[®] Web site at Neurology.org). The final sample included 584 subjects. TMT-B time was used as a sensitive test for SVD-related processing speed impairment in the primary analysis.³ We furthermore included a reaction time test (Vienna Test System, Schuhfried GmbH, Mödling, Austria), the digit span test (Wechsler Adult Intelligence Scale), and the Wisconsin Card Sorting Test (compound score for completed categories, nonperseverative errors, and perseverative errors). Raw test scores from the entire ASPS/ASPS sample (including those without neuroimaging data, $n = 1353$) were used to calculate z scores, adjusted for age and education (table e-1). See e-Methods and table 1 for demographic information.

Standard protocol approvals, registrations, and patient consents. The ethics committee of the Medical University of Graz approved the study. Written informed consent was obtained from all subjects.

MRI and segmentation of WMH. MRI scans were performed on 1.5T (Philips Medical Systems, Hamburg, Germany, $n = 304$) or 3T (Siemens Magnetom Tim Trio, Erlangen, Germany,

$n = 297$) systems. See table e-2 for acquisition parameters. Binary WMH¹ maps were created from fluid-attenuated inversion recovery images by 2 experienced raters (S.S. and S.R.) using a home-written IDL program (Exelis Visual Information Solutions, Boulder, CO), which is based on region growing and local thresholding following manual selection. Individual WMH maps were transformed into Montreal Neurological Institute 152 standard space by a lesion-masking approach utilizing tools from the Functional MRI of the Brain Software Library (FSL, version 4.1, e-Methods), as previously described.⁵ A corresponding analysis of lacunes was impossible because of their low prevalence (only 11 subjects had at least one lacune). Supratentorial brain parenchymal fraction as a measure of brain atrophy could be assessed in a subset of 504 subjects using tools from FSL as previously described.⁴

Voxel-based lesion-symptom mapping. Nonparametric mapping⁶ was used to test whether TMT-B z scores were different between subjects with and without WMH in a given voxel. Voxels affected in fewer than 4% of subjects were not considered for analysis (figure e-1). False discovery rate control was used to correct for multiple comparisons. The analysis was repeated adding global WMH volume as covariate.

Bayesian network analysis. Regional volumes of WMH were calculated for all 20 white matter tracts of a diffusion tensor imaging-based atlas (JHU-ICBM DTI atlas; e-Methods, figures e-2 and e-3). Bayesian network analysis (bnlearn⁷ R package) was used to calculate and visualize the probabilistic relationships between regional lesion volumes, age, sex, vascular risk factors, and the z score of the neuropsychological test. The strength of network arcs was determined by 100 bootstrap replications and expressed the relative frequency of each arc in the networks learned after resampling (for details, see e-Methods).

RESULTS Frequency maps of WMH in the final sample of 584 subjects are shown in figure 1. VLSM identified multiple voxel clusters in which WMH were significantly related to a slower TMT-B performance. The majority of voxels was located bilaterally in the anterior thalamic radiation (ATR) and the forceps minor (Fmin) (figure 2A, table e-3). When controlling for global WMH volume, several voxels in the same white matter tracts remained significant.

We next analyzed the impact of regional lesion volumes within each of the 20 major white matter tracts. Bayesian network analysis revealed the regional lesion volumes in the left ATR and the Fmin to be directly connected to TMT-B performance (figure 2B). The structure of the network with all regional lesion volumes is shown in figure e-4. In multiple regression analysis, regional lesion volumes in the left ATR and the Fmin explained 1.8% of the variance in TMT-B z scores (R^2 adjusted = 0.018; $F = 6.32$; $df = 2,581$; $p = 0.0019$). In contrast, global WMH volume ($F = 3.35$; $df = 1,582$; $p = 0.068$) and brain parenchymal fraction ($F = 0.195$, $df = 1,503$; $p = 0.659$) did not predict TMT-B performance.

To explore the specificity of our findings, we further calculated Bayesian networks for reaction time, digit span, and the Wisconsin Card Sorting Test: the only robust connection was between lesions in the left ATR

Table 1 Characteristics of the study group

Characteristics	Imaging subgroup	Entire group
Demographic characteristics		
Participants, n	584	1,353
Age, y, mean (SD)	67.4 (9.2)	65.4 (8.6)
Education, y, mean (SD)	11.2 (2.7)	11.2 (2.7)
Female, n (%)	362 (62.0)	774 (57.2)
Vascular risk factors, n (%)		
Current smoker	74 (12.7)	169 (12.5)
Smoking history	230 (39.4)	555 (41)
Hypertension	404 (69.2)	838 (61.9)
Hypercholesterolemia	466 (79.8)	1113 (82.3)
Diabetes	64 (11.0)	151 (11.2)
Cognitive scores		
MMSE score, median (IQR)	28 (2)	28 (2)
TMT-B time, s, median (IQR)	115 (70)	111 (69)
TMT-B time, z score, mean (SD)	0.053 (0.94)	0 (1.00)
Reaction time, ms, median (IQR)	510 (128)	489 (136)
Reaction time, z score, mean (SD)	−0.092 (0.99)	0 (1.00)
Digit span raw score, median (IQR)	10 (2)	11 (3)
Digit span z score, mean (SD)	−0.186 (0.93)	0 (1.00)
WCST compound z score, mean (SD)	0.086 (0.69)	0 (1.00)
Imaging characteristics		
WMH volume, MNI, μ L, median (IQR)	9,300 (14,260)	NA
Patients with at least one lacune, n (%)	11 (1.9)	NA
Supratentorial BPF, median (IQR)	0.73 (0.05)	NA

Abbreviations: BPF = brain parenchymal fraction; IQR = interquartile range; MMSE = Mini-Mental State Examination; MNI = Montreal Neurological Institute 152 standard space; NA = not applicable; TMT-B = Trail Making Test, matrix B; WCST = Wisconsin Card Sorting Test; WMH = white matter hyperintensities.

Figure 1 White matter hyperintensities frequency map

Voxel-wise frequency of white matter hyperintensities (WMH) in the study group, superimposed onto the Montreal Neurological Institute 152 standard space T1 template.

and reaction time, another speed-dependent test (arc strength 71%) (figure e-5).

DISCUSSION The current study identified the left ATR and the Fmin as strategic white matter tracts for processing speed using 2 independent statistical approaches, both of which are observer-independent: VLSM and Bayesian network analysis. Graph-based methods account for interactions and intercorrelation between variables

such as lesion volumes in different white matter tracts (figure e-3), and, in fact, Bayesian network analysis independently confirmed the ATR and Fmin as direct predictors of processing speed performance.

Our results agree with findings obtained in younger subjects with hereditary SVD. Using similar methodology, we recently identified the ATR and Fmin as strategic white matter tracts in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.^{2,3} Our results are broadly in line with those from a recent study in patients with symptomatic atherosclerotic disease that identified the ATR and superior longitudinal fasciculus as strategic locations for impaired executive functions.⁸ However, that study used different neuropsychological tests and intercorrelations among variables were not taken into account, which makes their results difficult to compare.

Our findings highlight damage to frontal interhemispheric and thalamic projection fiber tracts as a predictor for processing speed performance. These tracts participate in or connect to frontal-subcortical neuronal circuits. An involvement of these circuits in processing speed and executive functioning is well-established.⁹ In light of the growing evidence for an involvement of these circuits in vascular cognitive impairment (VCI), the identification of strategic fiber tracts might have implications for the development of targeted pharmacologic approaches. The neurochemistry within frontal projections and subcortical circuits is complex, but a role of striatal cholinergic neurons in modulating thalamic activation is established.⁹ It is interesting that cholinergic treatment was associated with significant improvements in the TMT-B time and other executive

Figure 2 Significant associations with Trail Making Test B performance

(A) Voxel-based lesion-symptom mapping revealed clusters of voxels (red) in the bilateral anterior thalamic radiation (ATR) and forceps minor (Fmin). The presence of white matter hyperintensities (WMH) in these voxels was significantly related to a decrease in processing speed. Voxels remaining significant after adding global WMH volume (gWMHV) as a covariate are shown in orange. Significant voxels are located in the Fmin and ATR (derived from the JHU-ICBM diffusion tensor imaging atlas in Montreal Neurological Institute 152 space). (B) Direct predictors of Trail Making Test, matrix B (TMT-B) as determined by Bayesian network analysis on age, vascular risk factors, and regional WMH volumes in major white matter tracts. Percentages show the arc strength estimated through bootstrapping. Note that hypertension and diabetes both show a direct connection to TMT-B z scores as well as an indirect connection through the regional lesion volumes. Age showed a direct connection to the regional lesion volumes but not to TMT-B. Smoking and hypercholesterolemia were not connected with any of the other variables.

tests in a randomized controlled trial in patients with hereditary SVD.¹⁰ The main neurotransmitter in thalamocortical projections is glutamate and treatment with glutamate modulators has shown some benefits in patients with vascular dementia. Thus, modulating multiple transmitter systems in parallel might be a valuable treatment strategy for VCI, although this and potentially unspecific effects on other brain networks would need to be explored in a controlled trial.

As might be expected in a population of healthy elderly individuals, the variance explained by regional WMH volumes in strategic tracts was relatively small and much smaller than in hereditary SVD.^{2,3} Interestingly, our analysis showed an independent contribution of hypertension and diabetes to processing speed impairment, although the effects of these vascular risk factors seem in part mediated by the regional lesion volumes in strategic areas (figure 2B). We speculate that the effect of SVD-related damage to strategic structures will gain considerable importance in later disease stages with increasing lesion load and the occurrence of more severe tissue damage, in particular lacunes. Lacunes were only present in 11 subjects, again reflecting the mild stage of SVD. In addition, secondary effects on connected cortical regions¹¹ in advanced stages might play a crucial role in the development of cognitive deficits.¹² Future investigations in patients with more advanced WMH and clinical manifestations of SVD may determine the impact of strategic lesions in sporadic VCI.

This study has several strengths. First, there was a high number of community-dwelling, healthy elderly subjects with standardized MRI and neuropsychological data. Second, we obtained converging evidence from 2 independent statistical approaches, VLSM and graph-based methods. A common problem in multiple linear regression analysis is multicollinearity through highly correlated predictor variables. Bayesian network analysis overcomes this problem by looking at the conditional dependence structure of all variables.⁷ Potential limitations include the lack of specific measures of other age-related pathologies such as amyloid load. Moreover, our voxel-based lesion symptom mapping approach focused on brain regions frequently affected by SVD lesions. Less frequently affected brain regions with strategic importance might therefore not have been captured. The use of binary lesion masks for WMH might be another limitation. Quantitative measures of white and gray matter pathology such as diffusion tensor imaging could be even more suited to assess ischemic damage caused by SVD and the impact of lesion location on cognition.

AUTHOR CONTRIBUTIONS

Dr. Düring: study design, data analysis, drafting the manuscript. Dr. Gesierich: data analysis, statistical analysis, drafting the manuscript. Dr. Seiler: data collection, data analysis. L. Pirpamer: data processing, data analysis. Dr. Gonik: data analysis, statistical analysis. Dr. Hofer: data collection, data analysis.

Dr. Jouvent: data collection, revising the manuscript. Dr. Duchesnay: revising the manuscript. Dr. Chabriot: revising the manuscript. Dr. Ropele: data collection, data analysis, revising the manuscript. Dr. Schmidt: study supervision, revising the manuscript. Dr. Dichgans: study conceptualization, study supervision, revising the manuscript.

STUDY FUNDING

Supported by the Vascular Dementia Research Foundation, the German Center for Neurodegenerative Diseases (DZNE), an FP6 ERA-NET NEURON grant (01 EW1207), Fondation Leducq (Transatlantic Network of Excellence on the Pathogenesis of Small Vessel Disease of the Brain), and the Austrian Science Fund projects P20103 and I904.

DISCLOSURE

M. Düring received travel expenses for lectures from the United Leukodystrophy Foundation, the European Stroke Conference, and Kenes International. B. Gesierich, S. Seiler, L. Pirpamer, M. Gonik, E. Hofer, E. Jouvent, and E. Duchesnay report no disclosures relevant to the manuscript. H. Chabriot served on scientific advisory boards of trials for Lundbeck, Servier, and Janssen and serves as an editorial board member of *Cerebrovascular Diseases*. S. Ropele reports no disclosures relevant to the manuscript. R. Schmidt receives research support from the Austrian Science Fund. He received travel expenses and honoraria for lectures from Pfizer, Novartis, Janssen, Merz Austria, Lundbeck, and Ever Pharma. M. Dichgans receives research support from the German Research Foundation (DFG), German Federal Ministry of Education and Research (BMBF), the European Union (EU FP6 and FP7), Vascular Dementia Research Foundation, Corona Foundation, and Jackstädt Foundation. He received travel expenses and honoraria for lectures from Bayer Vital, Boehringer Ingelheim Pharma, Heel, Bristol-Meyer Squibb, Lundbeck, Sanofi-Aventis, Ever Pharma, and Shire as well as for educational activities not funded by industry, received honoraria for articles for Thieme, UpToDate, and Kohlhammer, serves as an editor for *Stroke*, the *International Journal of Stroke*, the *Journal of Neurochemistry*, and as an editorial board member of *Cerebrovascular Diseases*, and serves as a consultant for Bayer Vital, Boehringer Ingelheim, Bristol-Meyer Squibb, Ever Pharma, and Heel. Go to Neurology.org for full disclosures.

Received September 30, 2013. Accepted in final form January 21, 2014.

REFERENCES

1. 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.
2. Düring M, Gonik M, Malik R, et al. Identification of a strategic brain network underlying processing speed deficits in vascular cognitive impairment. *Neuroimage* 2012; 66C:177–183.
3. Düring 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.
4. Schmidt R, Ropele S, Enzinger C, et al. White matter lesion progression, brain atrophy, and cognitive decline: the Austrian Stroke Prevention Study. *Ann Neurol* 2005; 58:610–616.
5. Düring M, Csanadi E, Gesierich B, et al. Incident lacunes preferentially localize to the edge of white matter hyperintensities: insights into the pathophysiology of cerebral small vessel disease. *Brain* 2013;136:2717–2726.
6. Rorden C, Bonilha L, Nichols TE. Rank-order versus mean based statistics for neuroimaging. *Neuroimage* 2007;35: 1531–1537.
7. Scutari M. Learning Bayesian networks with the bnlearn R Package. *J Stat Soft* 2010;35:1–22.
8. Biesbroek JM, Kuijff HJ, van der Graaf Y, et al. Association between subcortical vascular lesion location and cognition:

- a voxel-based and tract-based lesion-symptom mapping study: The SMART-MR study. *PLoS One* 2013;8:e60541.
9. Tekin S, Cummings JL. Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an update. *J Psychosom Res* 2002;53:647–654.
 10. Dichgans M, Markus HS, Salloway S, et al. Donepezil in patients with subcortical vascular cognitive impairment: a randomised double-blind trial in CADASIL. *Lancet Neurol* 2008;7:310–318.
 11. Duering M, Righart R, Csanadi E, et al. Incident subcortical infarcts induce focal thinning in connected cortical regions. *Neurology* 2012;79:2025–2028.
 12. Righart R, Duering M, Gonik M, et al. Impact of regional cortical and subcortical changes on processing speed in cerebral small vessel disease. *Neuroimage Clin* 2013;2:854–861.

Enjoy Big Savings on NEW 2014 AAN Practice Management Webinars Subscriptions

The American Academy of Neurology offers 14 cost-effective Practice Management Webinars you can attend live or listen to recordings posted online. AAN members can purchase one webinar for \$149 or subscribe to the entire series for only \$199. *This is new pricing for 2014 and significantly less than 2013*—and big savings from the new 2014 nonmember price of \$199 per webinar or \$649 for the subscription. Register today for these and other 2014 webinars at AAN.com/view/pmw14:

April 8 – How PQRS Quality Measures Will Inform Future Medicare Value-based Payments

May 13 – Measuring and Improving Your Patients' Experience

June 18 – Using Practice Benchmarking Analytics to Improve Your Bottom Line

Earn 20 CME Credits Toward MOC with New NeuroPISM Modules

Choose from the latest lineup of quality modules to join the AAN's exclusive performance improvement programs designed to help you address both the Performance in Practice (PIP) and Continuing Medical Education (CME) components of Maintenance of Certification (MOC).

- **NEW! Distal Symmetric Polyneuropathy (DSP)** includes **eight quality measures**, addressing accurate and appropriate evaluation/monitoring of DSP and associated symptoms to guide treatment options, patient safety, and best practices to assist patients in managing their pain and improving quality of life
- **Acute Stroke** addresses **six quality measures**, including deep vein thrombosis prophylaxis (DVT) for ischemic stroke or intracranial hemorrhage, discharged on antiplatelet therapy, dysphagia screening, rehabilitation service considerations, and more
- **Dementia** includes **10 quality measures** addressing underuse of effective services and patient-centered care strategies, and patient safety issues

Learn about all of the other available modules and purchase yours today:

www.aan.com/view/neuropi