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

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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 lesions[1] 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.

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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

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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/ASPFS 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 WMH[1] 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 mapping[6] 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 (bnlearn[7] *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).

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, μL, 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

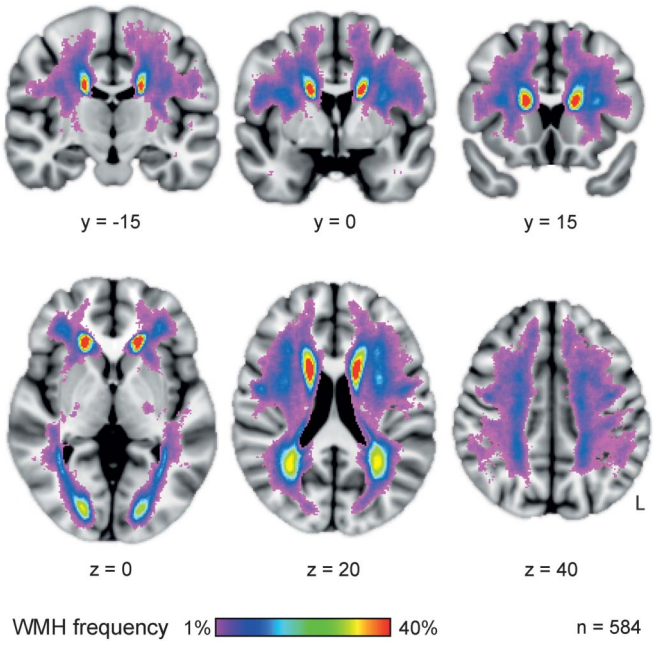
Abbreviations: BPF = brain parenchymal fraction; IQR = interquartile range; MMSE = Mini-Mental State Examination; MNI = Montreal Neurological Institute 152 standard space; NA = not applicable; TMT-B = Trail Making Test, matrix B; WCST = Wisconsin Card Sorting Test; WMH = white matter hyperintensities.

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

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.

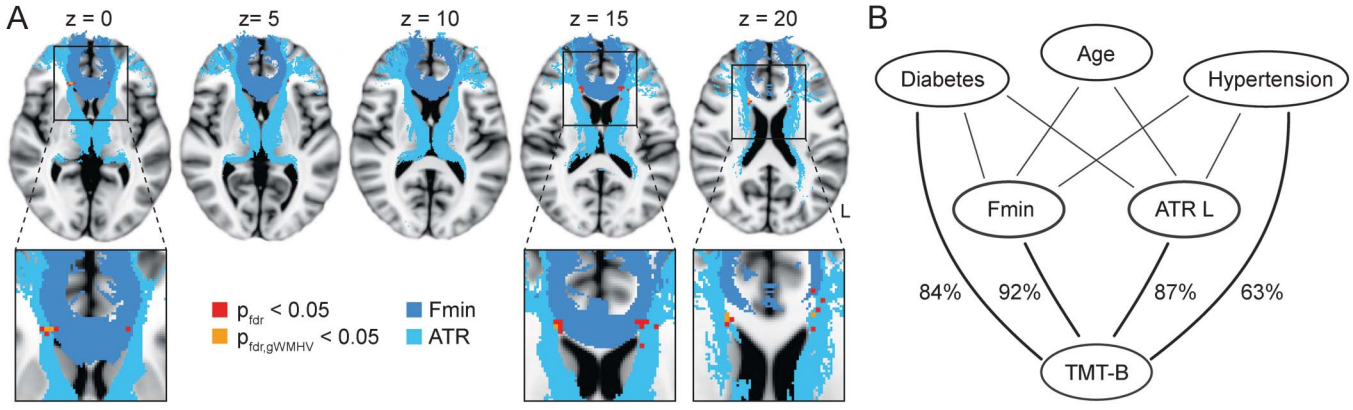
and reaction time, another speed-dependent test (arc strength 71%) (figure e-5).

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 regions[11] 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. Duering: 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. Chabriat: 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.

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