Interplay of White Matter Hyperintensities, Cerebral Networks, and Cognitive Function in an Adult Population

Radiology

Interplay of White Matter Hyperintensities, Cerebral Networks, and Cognitive Function in an Adult Population: Diffusion-Tensor Imaging in the Maastricht Study

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Background: Lesions of cerebral small vessel disease, such as white matter hyperintensities (WMHs) in individuals with cardiometabolic risk factors, interfere with the trajectories of the white matter and eventually contribute to cognitive decline. However, there is no consensus yet about the precise underlying topological mechanism.

Purpose: To examine whether WMH and cognitive function are associated and whether any such association is mediated or explained by structural connectivity measures in an adult population. In addition, to investigate underlying local abnormalities in white matter by assessing the tract-specific WMH volumes and their tract-specific association with cognitive function.

Materials and Methods: In the prospective type 2 diabetes–enriched population-based Maastricht Study, structural and diffusion-tensor MRI was performed (December 2013 to February 2017). Total and tract-specific WMH volumes; network measures; cognition scores; and demographic, cardiovascular, and lifestyle characteristics were determined. Multivariable linear regression and mediation analyses were used to investigate the association of WMH volume, tract-specific WMH volumes, and network measures with cognitive function. Associations were adjusted for age, sex, education, diabetes status, and cardiovascular risk factors.

Results: A total of 5083 participants (mean age, 59 years ± 9 [standard deviation]; 2592 men; 1027 with diabetes) were evaluated. Larger WMH volumes were associated with stronger local (standardized β coefficient, 0.065; $P < .001$), but not global, network efficiency and lower information processing speed (standardized β coefficient, −0.073; $P < .001$). Moreover, lower local efficiency (standardized β coefficient, −0.084; $P < .001$) was associated with lower information processing speed. In particular, the relationship between WMHs and information processing speed was mediated (percentage mediated, 7.2% [95% CI: 3.5, 10.9]; $P < .05$) by the local network efficiency. Finally, WMH load was larger in the white matter tracts important for information processing speed.

Conclusion: White matter hyperintensity volume, local network efficiency, and information processing speed scores are interrelated, and local network properties explain lower cognitive performance due to white matter network alterations.

Online supplemental material is available for this article.

Cerebral small vessel disease (cSVD) is a major cause of vascular cognitive impairment (1). The characteristic lesions, of which white matter hyperintensities (WMHs) are the most prevalent, interfere with the trajectories of the white matter and may disrupt the connections between distributed gray matter regions. Well-known risk factors for the occurrence of these lesions are of cardiometabolic origin and include diabetes, hypertension, abdominal obesity, dyslipidemia, physical inactivity, and aging (2,3). The changes in white matter connectivity may contribute to general cognitive decline and decline in various specific cognitive domains, including information processing speed, executive function and attention, and memory (3,4). Cognitive function generally relies on the integrity of large-scale structural white matter connections of the underlying brain network (5).

Previously it was shown in a population-based study of elderly individuals that periventricular WMHs are related to worse cognitive function in contrast to more deeply located, subcortical WMHs (6). This finding

Abbreviations

cSVD = cerebral small vessel disease, IQR = interquartile range, WMH = white matter hyperintensity

Summary

White matter hyperintensity volume, local efficiency, and information processing speed scores are interrelated, and local network alterations as response to white matter abnormality explain detriments in cognition.

Key Results

- In a prospective study of 5083 participants in the Maastricht Study, white matter hyperintensity (WMH) volumes were associated with higher local network efficiency ($P < .001$) and lower information processing speed scores ($P < .001$).
- The relationship between WMH volume and information processing speed was partly mediated by the local network efficiency.
- Larger WMH load in white matter tracts important for information processing was associated with cognitive slowing.

is of interest because periventricular WMHs are located in areas with a high density of long-association white matter tracts that connect various widely distributed cortical regions supporting multiple cognitive functions. Similarly, initially it was thought that only the extensive level of WMH load would impair cognitive function, whereas currently it is clear that cardiovascular risk factors are associated with cSVD and cognitive performance (7).

Previous studies provided some insight into the mechanisms underlying cSVD-related cognitive decline (8–10). However, the precise topological manner in which white matter connectivity is disrupted, how cSVD contributes, and, consequently, how strong cognitive function is affected remain unknown. Similarly, it is unclear to what extent variations in locations of cSVD lesions in a population affect cognitive function. To unravel these interrelations, more information about the underlying local and tract-specific characteristics of the white matter network is needed.

The Maastricht Study provides the opportunity to investigate the associations between cSVD MRI markers and cognitive function in a large population with extensive availability of cardiometabolic risk factors. Therefore, the aim of the present study was to investigate whether cSVD lesions and cognitive function are associated and whether this association is mediated or explained by structural connectivity measures (ie, global and local network efficiency). To investigate underlying local changes in white matter, we assessed the tract-specific WMH volumes in the three types of white matter tracts (ie, association, projection, and commissural tracts) and their tract-specific association with cognitive function.

Materials and Methods

The Maastricht Study

We used data from the Maastricht Study, an observational prospective population-based cohort study. The rationale and methodology have been described previously (7). In brief, the study focuses on the cause, pathophysiology, complications, and comorbidities of type 2 diabetes and is characterized by an extensive phenotyping approach. Eligible for participation were all individuals aged 40–75 years living in the southern part of the Netherlands. Participants were recruited through mass media campaigns, from the municipal registries, and from regional Diabetes Patient Registry by mail. Recruitment was stratified according to known type 2 diabetes status, with an oversampling of individuals with type 2 diabetes, for reasons of efficiency. The present report includes cross-sectional data from the first 7689 participants, who completed the baseline survey between November 2010 and December 2017. The examinations of each participant were performed within a time window of 3 months. MRI measurements were obtained from December 2013 to February 2017. A total of 5547 participants were invited to undergo MRI; 464 were excluded owing to contraindications (Appendix E1 [online]), and 5083 participants had complete data without artifacts (Fig 1). The study was approved by the institutional medical ethical committee (NL31329.068.10) and the Dutch Ministry of Health, Welfare and Sports (permit 131088–105234-PG). All participants gave written informed consent. Although the data used in this study were derived from the Maastricht Study, restrictions apply to the availability of these data, which were used under license for the current study. Data are, however, available from the authors on reasonable request and with permission of the Maastricht Study management team.

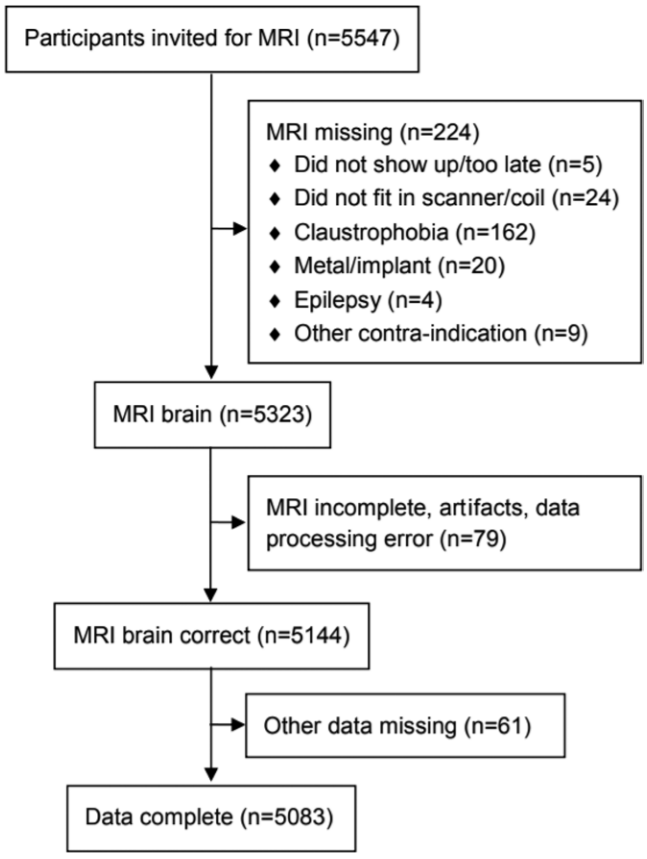

Figure 1: Flowchart of study population.

MRI Scans

MRI was performed with a 3-T scanner (Magnetom Prisma^{fit} Syngo MR D13D; Siemens Healthcare, Erlangen, Germany) using a 64-element head and neck coil. A three-dimensional T1-weighted magnetization-prepared rapid acquisition gradient-echo sequence (repetition time msec/echo time msec/inversion time msec, 2300/2.98/900; 176 slices; 256 × 240 matrix; 1.00-mm voxel size) was performed for anatomic reference. Diffusion-weighted MRI consisted of a diffusion-sensitized echo-planar imaging sequence (repetition time msec/echo time msec, 6100/57; 65 slices; 100 × 100 matrix; 2.00-mm voxel size; 64 diffusion sensitizing gradient directions [b = 1200 sec/mm^2]) with three images with a b value of 0.

Image Preprocessing

Ninety-four regions were defined with standard atlas software (Automated Anatomical Labeling Atlas 2) (11). After transformation (12), images were segmented into gray and white matter, WMH volume and intracranial volume were calculated, and cSVD lesions were identified (13) (Appendix E2 [online]). Periventricular WMHs were automatically defined as WMHs less than 3 mm from the cerebrospinal fluid in the ventricles, and deep WMHs as WMHs 3 mm or more from the cerebrospinal fluid in the ventricles (14). We focused on WMH volume, as WMHs are prominent in aging and centrally and deeply located in the cerebrum (analyses for periventricular and deep WMHs separately are provided in Tables E1, E2, and E4 [online]) (15). Diffusion-weighted MRI analysis consisted of tractography as described previously (12).

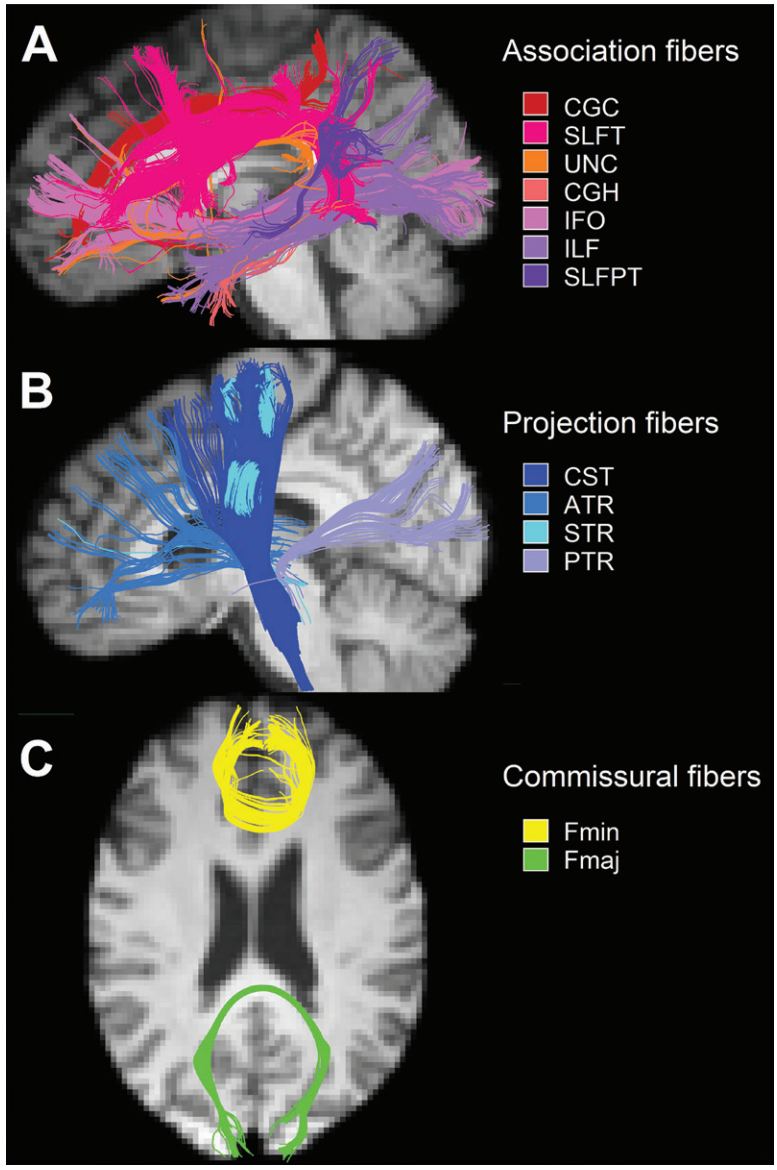

Figure 2: Three orthogonal views of 13 preselected white matter tracts acquired with automated atlas-guided tract reconstruction. *A*, MRI scan shows long association tracts for cingulum of cingulate gyrus (CGC), hippocampal part of cingulate gyrus (CGH), fronto-occipital fasciculus (IFO), inferior longitudinal fasciculus (ILF), parietal part of superior longitudinal fasciculus (SLFPT), temporal part of superior longitudinal fasciculus (SLFT), and uncinate fasciculus (UNC). *B*, MRI scan shows projection tracts for cortico-spinal tract (CST), anterior thalamic radiation (ATR), posterior thalamic radiation (PTR), and superior thalamic radiation (STR). *C*, MRI scan shows commissural tracts for forceps major (Fmaj) and forceps minor (Fmin).

White Matter Networks

Graph measures served to describe the network topology (15–17) by means of specialized software (Brain Connectivity Toolbox, version 2017–15–01) (18). Local efficiency was calculated as the inverse of the average shortest path connecting all neighbors of a region (excluding that region) and determines a network's resistance to failure at small scale. Global efficiency was determined based on the inverse of the average shortest path length calculated over the entire brain and quantifies the exchange of information on the whole network scale (19). In addition, whole brain node degree was calculated as the average number of connections per region. Subsequent steps were calculation of a standard network frame by means of proportional sparsity thresholding (80%) and normalization of the network measures to random networks (12).

White Matter Tract Segmentation

We determined the spatial distribution of WMHs and the WMH volumes of a number of well-known tracts with automated atlas-guided tract reconstruction (20) (Fig 2). Among the selected tracts are long association, projection, and commissural tracts (21). Volumes were merged for bilateral tracts. We transformed an atlas with 130 gray and white matter regions to diffusion space (22) and selected for each tract a specific subset of streamlines (20). Individual WMH maps transformed to diffusion space were used to determine the WMH volume traversed by the selected tracts (a flowchart with processing steps is shown in Figure E1 [online]).

Cognitive Performance

Cognitive performance was assessed by using a concise neuropsychological test battery (23). Information processing speed

was primarily reported, as it captures complex cognitive functioning (24), affects various major tracts simultaneously (25), and is strongly impaired in cSVD (10). Detailed descriptions of the tests and other cognitive domain scores are provided in Appendix E3 (online).

Statistical Analysis

Multivariable linear regression.—Multivariable linear regression was used to investigate the association of (tract-specific) WMH volume and structural connectivity with cognitive function. Analyses were adjusted for age, sex, education level, MRI patch update, and intracranial volume (the latter only in models with WMH volume, as network measures were already adjusted for intracranial volume) (model 1). Subsequent analyses were adjusted for diabetes status (model 2) and body mass index, ratio of total cholesterol to high-density lipoprotein level, systolic blood pressure, lipid-modifying and antihypertensive medication, and prior cardiovascular disease (model 3). Skewed variables (WMH volumes) were log10 transformed. $P < .05$ was considered to indicate a statistically significant difference. Interaction terms with sex and diabetes status were incorporated in the fully adjusted model (model 3). All analyses were performed with commercial software (SPSS version 23.0; IBM, Armonk, NY).

Mediation analysis.—Mediation analysis was used to test whether alterations in structural connectivity are on the potential causal pathway of the association between WMH volume and cognition, as it is biologically plausible that the white matter network is affected by WMHs (more details can be found in Appendix E4 [online]). For this, we used bootstrapping (5000 samples) to calculate bias-corrected 95% CIs with the PROCESS statistical package for SPSS (26). Analyses were fully adjusted (model 3).

Results

General Characteristics of the Study Population

The Table shows the general characteristics of the study population, which consisted of 5083 individuals (Fig 1) with a mean age of 59 years ± 9 (standard deviation); 2491 of the 5083 participants (49%) were women and 1027 (20%) had type 2 diabetes (oversampled by design). Of the 5547 participants invited to undergo MRI, 224 were excluded due to missing data (five did not show up or were too late for MRI; 24 did not fit in the scanner or coil; 162 had claustrophobia; 20 had metal implant; four had epilepsy; and nine had other contraindications to MRI or known brain abnormalities). MRI brain assessment was performed in 5323 participants, but 79 of them did not fulfill the whole scanning protocol or the data contained artifacts or other data processing errors. Of 5144 participants with correct MRI brain data available, 61 had other data missing, which led to a final total of 5083 participants with complete data.

White Matter Hyperintensities

Median WMH volume was 0.22 mL (interquartile range [IQR], 0.07–0.70 mL); in 19% of the participants the total WMH volume was greater than or equal to 1 mL, and 44% had a Fazekas score greater than or equal to 1. Cerebral microbleeds and lacunar infarcts were less prevalent (in 10% and 4%, respectively). In Figure 3, *B*, the spatial distribution of WMHs is depicted. Volumes of periventricular WMHs, near the lateral ventricles, were approximately three times larger compared with deep WMHs, located distant from the lateral ventricles in the subcortical white matter (Table).

In the connectogram in Figure 4, the 100 connections between automated Anatomical Labeling Atlas 2 regions with the largest difference in tract volume between subgroups with Fazekas scores of 0 and greater than or equal to 1 are depicted. This figure shows that in both hemispheres, especially in the short connections between cortical regions located close to the corpus callosum, participants with WMHs have smaller tract volumes. Connections between the left and right deep gray matter regions and cingulate cortex have larger tract volumes in participants with WMHs.

Association between WMH volumes and cognitive function.—Larger WMH volumes were associated with lower information processing speed scores (standardized β coefficient, −0.073 [95% CI: −0.101, −0.046]; $P < .001$) after adjustment for demographic and cardiovascular risk factors (model 3, Table E1 [online]). The associations were present for periventricular as well as deep WMHs.

Association between WMH volumes and network measures.—Larger WMH volumes were associated with higher local network efficiency (standardized β coefficient, 0.065 [95% CI: 0.035, 0.096]; $P < .001$), but not with whole brain node degree (standardized β coefficient, −0.027 [95% CI: −0.058, 0.003]; $P = .08$) and global efficiency (standardized β coefficient, −0.011 [95% CI: −0.044, 0.021]; $P = .48$). A comparable association was found for both periventricular and deep WMHs (Table E2 [online]).

Association between network measures and cognition.—Higher whole brain node degree (standardized β coefficient, 0.113 [95% CI: 0.089, 0.1438]; $P < .001$) and lower local efficiency (standardized β coefficient, −0.084 [95% CI: −0.109, −0.059]; $P < .001$) were associated with higher information processing speed scores. Global efficiency was not associated with information processing speed scores (standardized β coefficient, −0.014 [95% CI: −0.038, 0.010]; $P = .25$) (Table E3 [online]).

Mediation analysis.—Local efficiency mediated for 7.2% (95% CI: 3.5, 10.9, $P < .05$; indirect effect: standardized β coefficient, −0.005 [95% CI: −0.009, −0.002], $P < .05$) the association between WMH volume and information processing speed (Fig 5, Table E4 [online]).

Characteristics in type 2 diabetes.—The population-based design, with oversampling of participants with type 2 diabetes, enabled an accurate comparison of individuals with and individuals without diabetes. Participants with diabetes had ap-

Characteristics of the Study Population

Characteristic	Value (n = 5083)
Demographic characteristics	
Age (y)*	59 ± 9
No. of women	2491 (49)
Education level	
Low (none, primary education incomplete, primary education, lower vocational education)	1627 (32)
Intermediate (intermediate vocational education, higher secondary education)	1423 (28)
High (higher professional education, university education)	2033 (40)
Cardiovascular risk factors	
Body mass index (kg/m^2)*	26.6 ± 4.2
Waist circumference (cm)*	94.1 ± 13.0
Systolic blood pressure (mm Hg)*	132.9 ± 17.3
Diastolic blood pressure (mm Hg)*	75.5 ± 9.7
Type 2 diabetes	1027 (20)
Hemoglobin A_{1c} level (mmol/mol)*	38.9 ± 8.9
Hypertension	2541 (50)
Ratio of total cholesterol to high-density lipoprotein*	3.6 ± 1.2
History of cardiovascular disease	661 (13)
Medication use	
Antihypertensive medication	1728 (34)
Lipid-modifying medication	1423 (28)
Lifestyle factors	
Alcohol use	
None	864 (17)
Low (≤7 glasses per wk for women; ≤14 glasses per wk for men)	2999 (59)
High (>7 glasses per wk for women; >14 glasses per wk for men)	1220 (24)
Smoking status	
Never	1982 (39)
Former	2491 (49)
Current	610 (12)
Dutch Healthy Diet Index score*	84.2 ± 15.0
Total physical activity (h/wk)*	14.1 ± 8.0
Mild-to-vigorous physical activity (h/wk)*	5.6 ± 4.4
Cognitive score†	
Mini-Mental State Examination total score (maximum score, 30)	29 (29–30)
Information processing speed	0.11 (−0.41 to 0.58)
Executive function and attention	0.09 (−0.43 to 0.61)
Memory function	0.09 (−0.60 to 0.75)
Cerebral small vessel disease characteristics	
Total WMH volume (mL)†	0.22 (0.07–0.70)
Periventricular WMH volume (mL)†	0.15 (0.04–0.48)
Deep WMH volume (mL)†	0.05 (0.01–0.20)
Fazekas score	
0	2836 (56)
1	1159 (23)
2	676 (13)
3	412 (8)
Cerebral microbleeds present	508 (10)
Cerebral lacunar infarcts present	218 (4)
Structural connectivity graph measures*	
Whole brain node degree	17.75 ± 0.36
Local efficiency	1.49 ± 0.04
Global efficiency	0.84 ± 0.03

Note.—Unless otherwise specified, data are numbers of patients, with percentages in parentheses. Detailed protocols of the general measurements are presented in Appendix E1 (online). WMH = white matter hyperintensity.

* Data are means ± standard deviations.

† Data are medians, with interquartile range in parentheses.

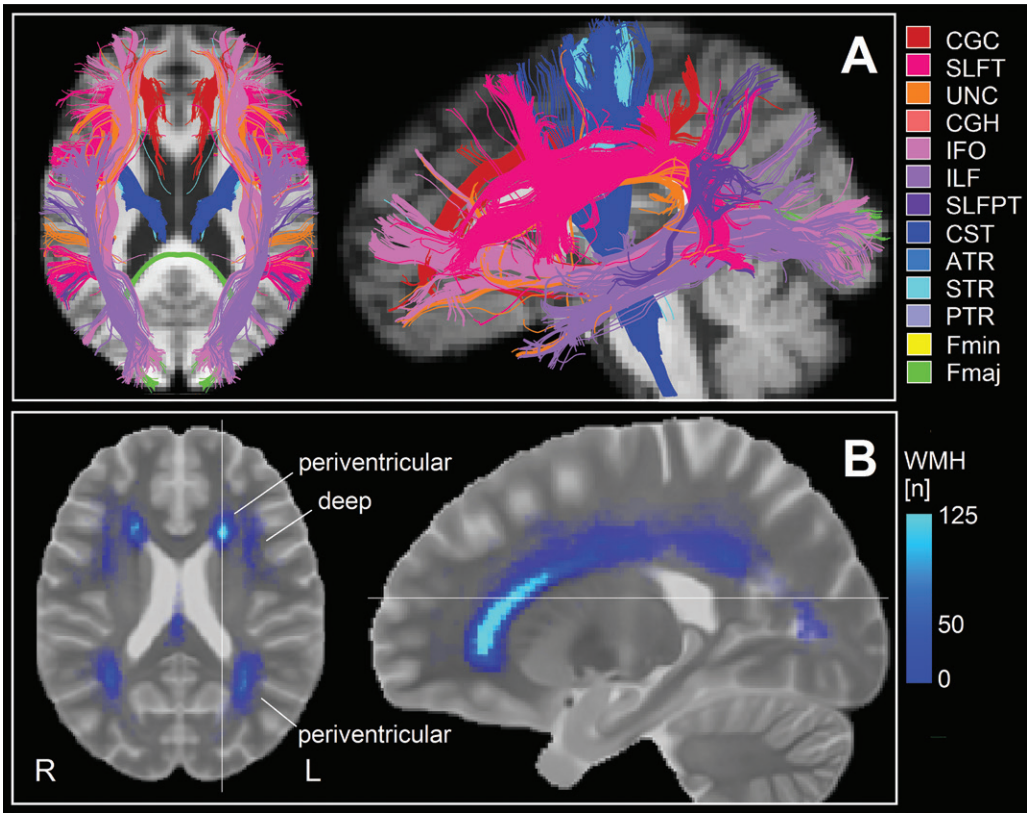

Figure 3: *A*, MRI scans demonstrate tracts with significant associations ($P < .05$) of tract-specific white matter hyperintensity (WMH) volume, with information processing speed scores, adjusted for age, sex, education, diabetes status, and cardiovascular risk factors (model 3). ATR = anterior thalamic radiation, cGC = cingulum of cingulate gyrus, CGH = hippocampal part of cingulate gyrus, CST = cortico-spinal tract, Fmaj = forceps major, Fmin = forceps minor, IFO = fronto-occipital fasciculus, ILF = inferior longitudinal fasciculus, PTR = posterior thalamic radiation, SLFPT = parietal part of superior longitudinal fasciculus, SLFT = temporal part of the superior longitudinal fasciculus, STR = superior thalamic radiation, UNC = uncinate fasciculus. *B*, WMH prevalence map of study sample. Note higher prevalence and overlap of white matter lesions in periventricular region, whereas deep lesions are more widespread. Colors indicate number of participants who had WMHs in that voxel.

proximately two times larger WMH volumes (median volume, 0.19 mL [IQR, 0.06–0.58] without diabetes vs 0.38 mL [IQR, 0.13–1.28] with diabetes) (27). Furthermore, participants with diabetes had slightly higher local efficiency (mean ± standard deviation, 1.51 ± 0.05 with diabetes vs 1.49 ± 0.04 without diabetes; $P < .01$) and slightly lower information processing speed scores (median, −0.20 [IQR, −0.80 to 0.29] with diabetes vs 0.18 [IQR, −0.32 to 0.62] without diabetes; $P < .01$) compared with participants without diabetes in the fully adjusted regression model (model 3). We did not find interactions with diabetes status or sex.

Tract-specific Analysis

For the majority of the tracts (nine of 12), a larger WMH volume was significantly associated with slower information processing, and a comparable effect was found for the other cognitive domains (Table E5, Fig E1, and Appendix E5 [online]).

Long association tracts.—We found the largest WMH volumes in the tracts fronto-occipital fasciculus and temporal part of the superior longitudinal fasciculus (respectively, 40% and 18% of the total WMH in the selected tracts). From Figure 3 it can be appreciated that the fronto-occipital fasciculus and temporal part of the superior longitudinal fasciculus (Fig 3, *A*) both cross the anterior and posterior horns, which are regions with a high WMH prevalence (Fig 3, *B*). For almost all association tracts (cingulum of cingulate gyrus, parietal and temporal part of superior longitudinal fasciculus, uncinate fasciculus [$P < .01$], fronto-occipital fasciculus, and inferior longitudinal fasciculus [$P < .05$]), larger WMH volumes (Fig 3, *A*) were, after adjustment for demographic and cardiovascular risk factors, still strongly associated with lower information processing speed.

Projection tracts.—We did not find large WMH volumes in the projection tracts. However, the WMH volume in the superior thalamic radiation covers approximately 7% of the total WMH volume over all selected tracts (Table E5 [online]). This tract traverses regions with WMHs that are mainly located in the deep subcortical structures of the frontal and parietal lobe. Larger WMH volumes in the superior thalamic radiation and corticospinal tract, but not in the anterior thalamic radiation and posterior thalamic radiation, were associated with lower information processing speed ($P < .01$).

Commissural tracts.—The forceps major and forceps minor have small absolute WMH volumes, which, however, cover a substantial part of their relatively small total tract volume (7% and 9%, respectively). The forceps major crosses the regions with high WMH prevalence located near the posterior horns, and the forceps minor near the anterior horns. Associations between WMH volumes and information processing speed were found only in the forceps major ($P < .01$). More details are provided in Table E5 (online).

Discussion

We set out to find interrelations between white matter hyperintensity (WMH) volumes, white matter connectivity, and domain-specific cognitive function in a large adult population with cardiometabolic risk factors. Larger WMH volumes were

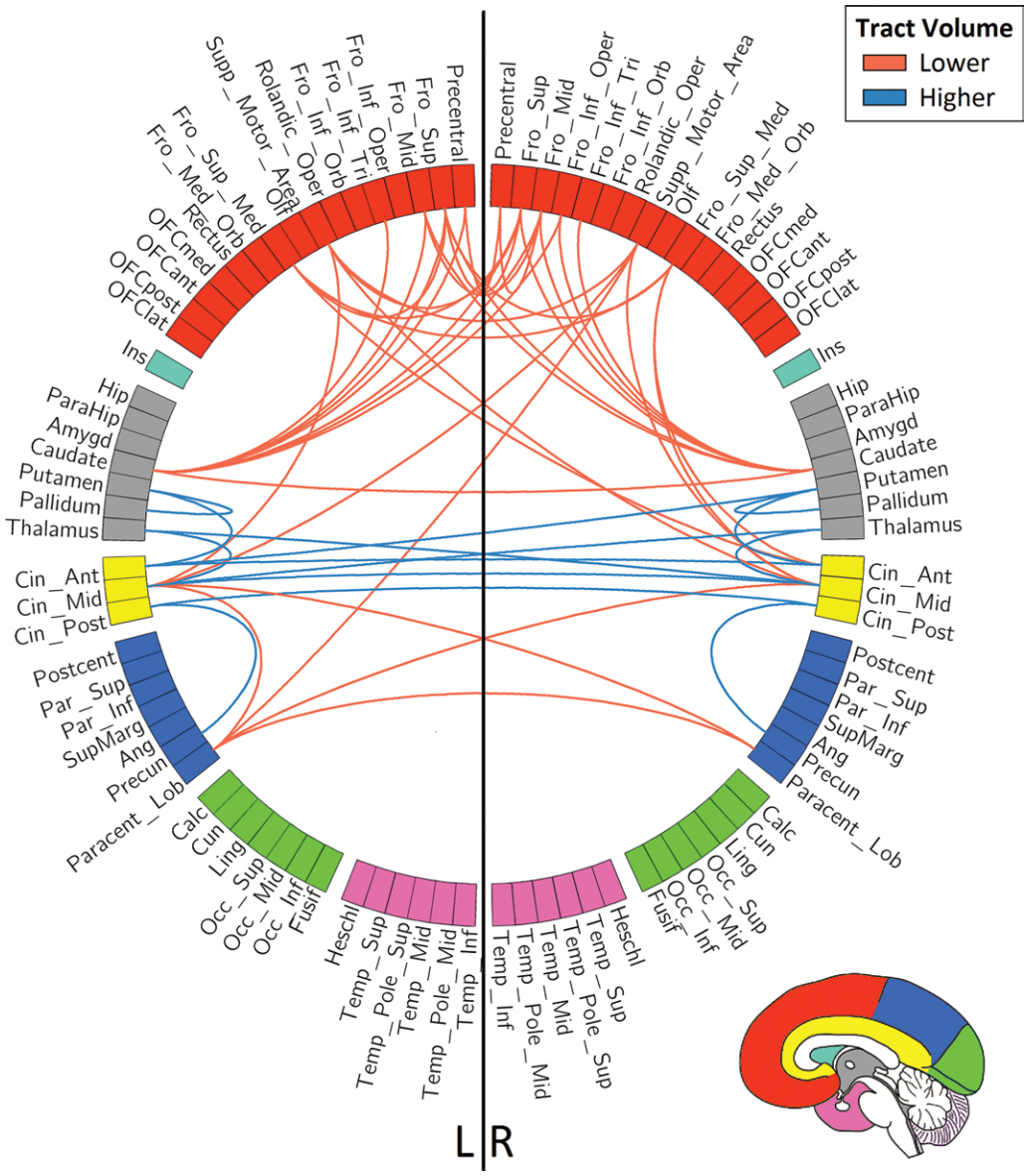

Figure 4: Connectogram qualitatively depicts 100 white matter tracts between Automated Anatomical Labeling Atlas regions with largest (absolute) difference in tract volume between groups based on Fazekas scores. Red lines indicate tracts with lower tract volumes in group with white matter hyperintensities (Fazekas score ≥1 vs 0), and blue lines indicate higher tract volumes.

associated with stronger local network efficiency and slower information processing. The relationship between WMHs and information processing speed was partly mediated by the local network efficiency. In addition, larger WMH load in white matter tracts important for information processing was associated with cognitive slowing.

In the white matter, the local but not the global network efficiency acted as a mediator between WMHs and cognitive slowing. WMHs are focally isolated lesions that disturb connections of specific tracts, whereas the global brain network topologic features are preserved. We found a higher local efficiency for more WMHs, which indicates that the local network organization is compensated for by use of alternative white matter pathways that strengthen connections (higher tract volume) with the neighboring regions (12).

Two previous studies found that both lower local and global efficiency were associated with lower processing and/or psychomotor speed and mediated the associations between MRI markers for cSVD and cognition (8,9). However, these studies involved participants with more severe (eg, symptomatic) cSVD as compared with our study population. In contrast, the current study comprises milder or commencing cSVD pathologic condition without obvious global network impairment but with local adaptations.

The majority of tracts with a substantial amount of WMHs reveal negative effects on information processing speed for higher WMH load. In this study, we focused on the cognitive domain information processing speed, as this is important for fluent execution of perceptual, cognitive, and psychomotor processes (28). Therefore, information processing speed is associated with the properties of connections between many distributed brain regions and does not appeal to highly distinctive tracts but more a variety of tracts (21,29,30).

To put the degree of the cognitive decline into perspective, a 0.51 mL larger WMH volume was equivalent to 10 years of cognitive aging in the association between WMH volume and information processing speed, whereas a 1.69 mL greater WMH was equivalent to 10 years of network aging in terms of local efficiency. This comparison suggests that the impact of WMHs on the local network topologic features is approximately three times stronger than would be expected for cognitive decline, which can be explained by compensatory network adaptations outside the lesions. Cerebral lacunar infarcts and microbleeds were less prominent in comparison with WMHs and also provided associations with both cognitive function and structural connectivity, as expected from the literature (8,31), although less evident than with WMHs. Participants with type 2 diabetes had larger WMH

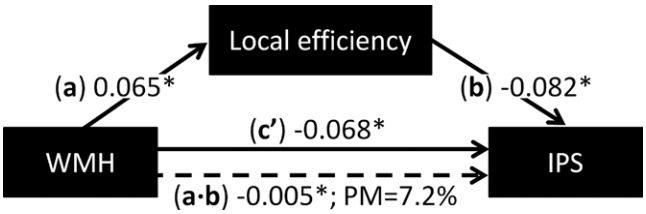

Figure 5: Diagram illustrates associations between white matter hyperintensity (WMH) volume, local network efficiency, and information processing speed (IPS) score, and mediation by local efficiency. Solid lines indicate direct effects (c′); dashed lines indicate indirect effects (a · b) and percentage mediated (percentage mediated [PM] = indirect/total = indirect/[indirect + total]). Associations are given as standardized regression coefficients (standardized β) and are adjusted for age, sex, education, intracranial volume, diabetes status, MRI patch update, body mass index, ratio of total cholesterol to high-density lipoprotein, systolic blood pressure, lipid-modifying and antihypertensive medication, and prior cardiovascular disease. * = $P < .01$.

volumes, higher local efficiency, and lower information processing speed scores compared with participants without type 2 diabetes. The lower cognitive scores were equivalent to 3.3 years of cognitive aging. For the other cardiometabolic risk factors, no clear effects were found (only marginal differences between models 2 and 3), likely because these risk factors already led to higher WMH volumes. In addition, previous studies reported associations of hypertension (32,33), visceral obesity (34), abnormal body mass index (33), and metabolic syndrome (2) with increased risk of having WMHs.

Strengths of this study were the large sample size, the population-based design, the extensive assessment of potential confounders, and the combined approach of whole brain network and tract-specific analysis to confirm the robustness of results. Furthermore, we used an automated atlas-guided tract reconstruction method based on whole brain fiber tractography instead of a diffusion-weighted MRI atlas coregistered to a structural image to determine tract volumes. There were also some limitations. First, the cross-sectional design of the study implies that no conclusions about temporality of alterations in WMH, network properties, and cognition can be made. Second, WMHs were expressed at locations that are typical for aging populations with cardiometabolic risk factors. Therefore, for the specific cognitive domains we are restricted to making inferences regarding the specific white tracts with the current distribution of WMHs and cannot make inferences regarding the susceptibility of other white matter regions, although the whole brain network analysis demonstrated widely distributed alterations. In line with this, standardized regression coefficients were small (<0.1), likely because of the relatively healthy population. The pathologic features of cSVD are rather limited, and cognition scores were relatively high. Therefore, the associations that were found indicate that the first signs of cSVD abnormalities already relate to alterations in the structural network organization and cognitive decrements.

In conclusion, we found that white matter hyperintensity (WMH) volume, local efficiency, and information processing speed scores are interrelated. More specifically, the detrimental effect of larger WMH volume on cognitive function was mediated by local efficiency. Locally, we found that larger WMH volumes in white matter tracts that are important for information processing were associated with cognitive slowing, which reflects cognitive decrements due to white matter pathologic features in aging individuals with cardiometabolic risk factors.

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