

Cardiovascular Risk Factors and Brain Health: Impact on Long-Range Cortical Connections and Cognitive Performance

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Background—Cardiovascular risk factor burden in the absence of clinical or radiological “events” is associated with mild cognitive impairment. Magnetic resonance imaging techniques exploring the integrity of neuronal fiber connectivity within white matter networks supporting cognitive processing could be used to measure the impact of cardiovascular disease on brain health and be used beyond bedside neuropsychological tests to detect subclinical changes and select or stratify participants for entry into clinical trials.

Methods and Results—We assessed the relationship between verbal IQ and brain network integrity and the effect of cardiovascular risk factors on network integrity by constructing whole-brain structural connectomes from magnetic resonance imaging diffusion images (N=60) from people with various degrees of cardiovascular risk factor burden. We measured axonal integrity by calculating network density and determined the effect of fiber loss on network topology and efficiency, using graph theory. Multivariate analyses were used to evaluate the relationship between cardiovascular risk factor burden, physical activity, age, education, white matter integrity, and verbal IQ. Reduced network density, resulting from a disproportionate loss of long-range white matter fibers, was associated with white matter network fragmentation ($r=-0.52$, $P<10^{-4}$), lower global efficiency ($r=0.91$, $P<10^{-20}$), and decreased verbal IQ (adjusted $R^2=0.23$, $P<10^{-4}$).

Conclusions—Cardiovascular risk factors may mediate negative effects on brain health via loss of energy-dependent long-range white matter fibers, which in turn leads to disruption of the topological organization of the white matter networks, lowered efficiency, and reduced cognitive function. (*J Am Heart Assoc.* 2018;7:e010054. DOI: 10.1161/JAHA.118.010054.)

Key Words: cardiovascular disease risk factors • connectome • diffusion-weighted imaging • graph theory

Brain health can be broadly defined as the physiological state in which sensorimotor and cognitive tasks are performed within a normal level that is comparable across healthy individuals. This definition can also be expanded to imply neurological functional reserve, that is, the ability to learn and adapt to new knowledge and challenges or to recover from neurological disease.

Currently, brain health is largely assessed in the context of clinical neuroscience through behavioral measures. Cognitive performance is assessed using standard paper-and-pencil

neuropsychological tests, whereas sensorimotor abilities are commonly assessed through a neurological examination.^{1,2} Likewise, neurological adaptation is measured through observation of learning rates or through recovery after brain injury.³⁻⁵

These behavioral measures provide some insight into the underlying biological phenomena that are fundamentally related to brain health. However, behavioral measures do not yield specific information about the exact underlying neuroanatomical mechanisms that constitute brain health and, as a result, are limited in their ability to predict performance or reserve, particularly in the context of neurological disease and subclinical changes, where identifying compromised neuroanatomical networks can be important for treatment considerations.

Cardiovascular risk factors, such as diabetes mellitus, hypertension, and hyperlipidemia are detrimental to general health and to cognition in particular. They have pervasive and profound effects on end-organ function and peripheral vasculature.⁶ Cardiovascular risk factors result in initial subtle brain structural changes and cognitive decline that may eventually lead to dementia.^{7,8} Likewise, the cumulative

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Clinical Perspective

What Is New?

- We demonstrate that cardiovascular risk factor burden is associated with the loss of long-range white matter fibers, which leads to the breakdown of complex network organization and subsequent cognitive decline.

What Are the Clinical Implications?

- With further validation, identification of the way compromised neuroanatomical networks relate to brain health, particularly in the context of neurological disease and dementia, may be important for diagnostic strategy and treatment interventions.

effects of microangiopathic changes and perivascular lipohyalinosis are commonly associated with white matter changes in the brain.⁹ Although white matter has lower metabolic needs, it is significantly more vulnerable to ischemic damage compared with gray matter. White matter receives less cerebrovascular perfusion¹⁰ and has a declining anaerobic resistance associated with aging.¹¹ Despite the well-known relationship between white matter susceptibility and ischemic damage, the mechanisms linking small-vessel disease, white matter network disruption, brain health, and cognitive decline are not well understood. Likewise, the impact of microangiopathic white matter loss on cognitive performance is not well defined in mild to moderate cases. Therefore, evidence of premorbid brain decline coupled with changes in brain structural integrity may be an early indicator of cognitive decline and dementia.

In this study we examined the question of whether cognitive function is related to cardiovascular risk factor burden and loss of network integrity, which can be understood as a biological measure of brain health.

We leveraged methodological advancements in systems and computational neurosciences related to the human brain connectome. The structural connectome is a map of all medium- to large-scale white matter connections across the entire brain derived from diffusion tensor magnetic resonance imaging (DTI). The connectome reveals regional pairwise brain connectivity between all defined brain regions and enables quantification of the topology of complex brain networks beyond gray or white matter atrophy, which may occur with healthy aging. The connectome is an individual map on which the topological brain network organization can be compared across individuals in the context of health or disease.¹² By providing a comprehensive overview of neuronal network organization, the brain connectome has been applied successfully to improve the understanding of several broad categories of neurological diseases such as epilepsy,

dementia, and movement disorders.¹³⁻¹⁶ However, it has not been evaluated thus far as a measure of brain health.

Individualized connectomes can be assessed with regard to their integrity and topological network organization, leveraging knowledge from network analyses. Global and regional properties can be assessed with regard to efficiency of transfer of information via network integration and segregation.¹⁷ We evaluated the association among cardiovascular risk factors, white matter integrity, and cognitive performance in a group of participants with varying cardiovascular risk factor burdens. Cognitive performance was evaluated using verbal IQ, calculated from the National Adult Reading Test-Revised,¹⁸ which has been standardized against other measures of intelligence (Wechsler Adult Intelligence Scale)¹⁹ and serves as an accurate probe of premorbid cognitive performance. Specifically, we evaluated whether cardiovascular risk factor burden would be associated with loss of fiber density, especially among short- or long-range white matter connections, whose structural integrity entails a continuum from lower to higher metabolic demand, respectively. We hypothesized that a high cardiovascular risk factor burden would be associated with a loss of energy-dependent long axonal projections, leading to lower verbal IQ. The confirmation of our hypothesis would lead to the proposal that white matter network architecture could provide a singular, quantifiable measure of overall brain health by using imaging connectomics.

Methods

Anonymized data used in this study will be made available to investigators who provide a written request to the corresponding author to analyze the data, indicating the study in which the data will be used.

Participants

We recruited 60 participants (47 female, mean age 55.1 ± 8.6 years) without a history of neurological or psychiatric diseases from the local community through advertisement. All participants were self-reported cognitively normal adults. Thirty-three participants did not have a history of cardiovascular risk factors (healthy control group), and 27 participants had previously been diagnosed with at least 1 cardiovascular risk factor: diabetes mellitus (14 participants), hyperlipidemia (18 participants), and hypertension (20 participants) (Table). Seven participants had been diagnosed with all cardiovascular risk factors (a group henceforth referred to as the cumulative morbidity group). These diagnoses were obtained through medical chart review. The Charlson Comorbidity Index²⁰ (CCI) was calculated for all participants. If participants reported a diagnosis of hypertension and/or hyperlipidemia, an extra point for each diagnosis was added

Table. Demographic Distribution

Characteristic	Without Cardiovascular Risk Factors (N=33)	With Cardiovascular Risk Factors		
		Diabetes Mellitus (N=14)	Hyperlipidemia (N=18)	Hypertension (N=20)
Age, y	52.2 (9.2)	59.4 (5.0)	59.2 (5.9)	59.3 (6.9)
Sex				
Female	29 (87.9%)	11 (78.6%)	11 (61.1%)	12 (60%)
Male	4 (12.2%)	3 (21.4%)	7 (38.9%)	8 (40%)
Race				
White	18 (54.6%)	3 (21.4%)	9 (50%)	7 (35%)
Black	15 (45.6%)	11 (78.6%)	9 (50%)	13 (65%)
Education, y	14.4 (2.0)	13.1 (2.0)	13.4 (1.9)	13.1 (2.1)
Behavioral measures				
Verbal IQ	111.95 (13.0)	99.34 (14.3)	105.05 (15.0)	102.74 (15.4)
CHAMPS	0.83 (0.29)	0.69 (0.32)	0.81 (0.29)	0.76 (0.32)

Data are given as mean (SD) or as N (%). CHAMPS indicates Community Healthy Activities Model Program for Seniors.

to the overall CCI score. All participants except 4 had at least a high school diploma. The study was approved by the Institutional Review Board at the Medical University of South Carolina, and all participants gave written informed consent.

Behavioral Evaluation

All participants underwent verbal performance assessment using the National Adult Reading Test-Revised¹⁸ as an estimator of premorbid cognitive function. Verbal intelligence was calculated in accordance with the National Adult Reading Test-Revised as shown:

$$\text{Estimated Verbal Scale IQ} = 128.7 - 0.89 \times \text{National Adult Reading Test-Revised errors}$$

All participants completed the Community Healthy Activities Model Program for Seniors,²¹ which was used as a measure for physical activity. All behavioral testing was performed within the same week as the neuroimaging assessment.

Image Acquisition

Imaging was performed on a Siemens (Munich, Germany) 3T Total imaging matrix trio MRI scanner located at the Medical University of South Carolina. We used T1-weighted, and diffusion images collected from each participant. T1 parameters were in the magnetization-prepared rapid gradient-echo sequence with 1-mm isotropic voxels, 256×256 matrix size, and a 9° flip angle. We used a 192-slice sequence with repetition time, TR=2250 milliseconds, T1=925 milliseconds, and echo time, TE=4.15 milliseconds. DTI parameters: twice-refocused echo-planar imaging b=0, 1000, 2000, 60 diffusion

encoding directions, TR=6100 milliseconds, TE=101 milliseconds, field of view=222×222 mm², matrix=82×82, 2.7-mm slice thickness, and 45 axial slices.

Structural Connectome Construction

Each participant's individual connectome was built from the neuroimaging data using the following steps: (1) T1-weighted images were segmented into probabilistic gray and white matter maps using the SPM12 unified segmentation-normalization; (2) each individual's gray matter map was divided into 1358 regions using the Atlas of Intrinsic Connectivity of Homotopic Areas brain atlas²²; (3) the gray matter parcellation maps were nonlinearly registered into the DTI space; (4) pairwise probabilistic DTI fiber tracking was computed for all possible pairs of gray matter regions (further details on the DTI tractography parameters below); (5) the weight of each pairwise connectivity link was determined based on the number of probabilistic streamlines connecting the gray matter region pair, corrected by distance traveled by each streamline and by the total volume of the connected regions; and (6) a weighted adjacency matrix **M** of size 1358×1358 was constructed for each participant with M_{ij} representing the weighted link between region of interest (ROI)_i and ROI_j.

Tractography was estimated using the Functional MRI of the Brain Diffusion Toolbox probabilistic method²³ with the Diffusion Toolbox BEDPOST software being used to assess default distributions of diffusion parameters at each voxel, and probabilistic tractography was performed using the Diffusion Toolbox probtrackX (parameters: 5000 individual pathways drawn through the probability distributions on principal fiber direction, curvature threshold set at 0.2, 200 maximum steps, step length 0.5 mm, and distance correction).

The waypoint mask was set as the white matter probabilistic map. The weighted connectivity between the regions i and j was defined as the number of probabilistic streamlines arriving at j region when i was seeded, averaged with the number of probabilistic streamlines arriving at i region when j was seeded. The connection weight was corrected based on the distance traveled by the streamlines connecting i and j (probtrackX's "distance correction"). The number of streamlines connecting each pair of regions was further divided by the sum of the volumes of these regions. In summary, each individual connectome was represented by a 1358×1358 matrix, where the nodes corresponded to the Atlas of Intrinsic Connectivity of Homotopic Areas anatomical regions and the edges to the structural connectivity between the nodes.

Network Analysis

Connectome Density

We assessed the overall connectivity of the networks by calculating the connectome density for each subject, which is defined as the ratio of all connections that exist in the network to all possible connections. Specifically, we assessed the total number of connections in the connectome and divided this by the number of possible connections. Thus, a density of 100% indicates a highly connected network in which all potential connections exist. We then compared the connectome density of participants with versus those without cardiovascular risk factors.

To determine which fibers were disproportionately lost, we calculated the percentage of short-, mid-, and long-range white matter fibers. First, we calculated the Euclidean distance between each pair of node centroids in each connectome and designated all fibers with lengths below the first quartile (lowest 25%) as short-distance fibers and all fibers with lengths above the third quartile (75% and above) long-distance fibers. Midrange fibers had lengths above the first quartile and below the third quartile (25% to 75%). We determined the proportion of all existing connections in each connectome that were either short-, mid-, or long-distance fibers. To determine the effect of cardiovascular risk factors on short-, mid-, and long-range white matter connectivity, we assessed differences in the percentage of short-, mid-, and long-distance fibers between participants with and those without cardiovascular risk factors.

Connectome Measures

We extracted graphed theoretical measures of network organization and efficiency using the Brain Connectivity Toolbox.²⁴

Each connectome was partitioned into communities or modules by optimizing the Newman modularity algorithm.²⁵ Modularity (Q) is a value that quantifies the strength of the network's modular organization by identifying groups of nodes that have stronger intracommunity coherence than

intercommunity coherence. Figure 1 provides a neuroanatomical overview of the parcellation scheme (Figure 1A through 1D), how modules are calculated (Figure 1E through 1H) in which ROIs belonging to the same module have the same

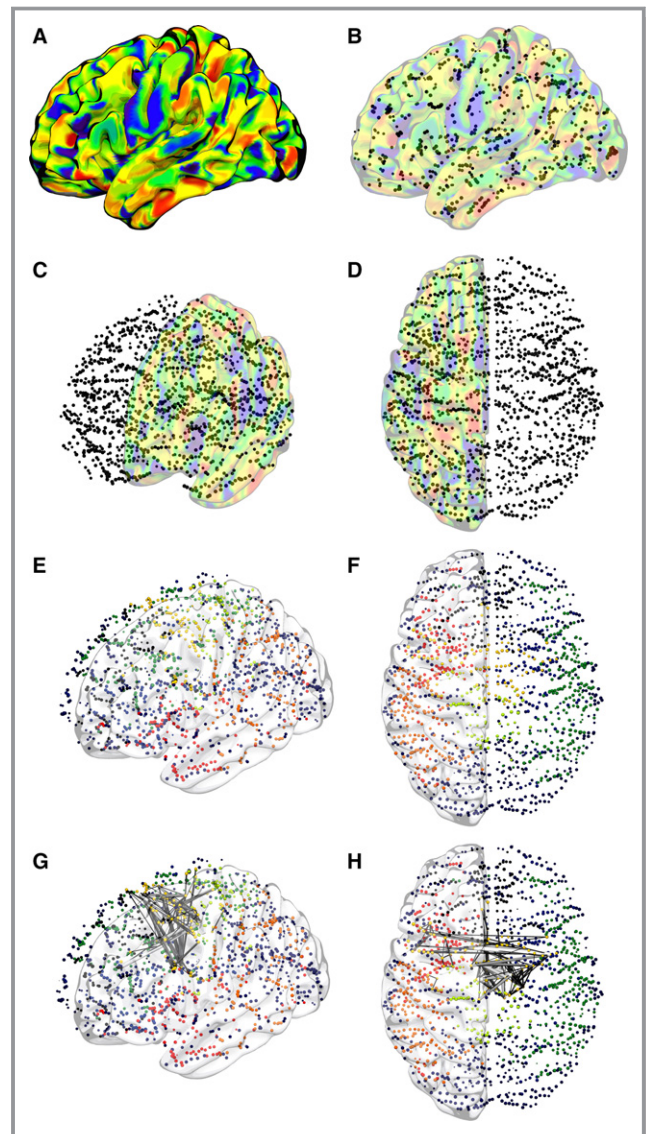


Figure 1. The gray matter regions are divided into 679 regions of interest (ROIs) in each hemisphere, corresponding to neuroanatomical boundaries defined by a parcellation atlas (A, where ROIs are indicated by different colors). To facilitate visualization of networks, each ROI can be represented by a sphere in the ROI's center of mass (B through D). Modularity is calculated by assessing the ROIs that are more closely integrated by their white matter networks and relatively segregated from the other surrounding modules. E through H, In the example of 1 subject, the ROIs that belong to the same module are represented using the same color (ie, all ROIs in yellow belong to the same module, which is different from the module containing ROIs in green, and so on). G and H, Edges corresponding to the white matter networks integrating 1 module (with ROIs in yellow), largely representing premotor circuitry.

color, and an example module and connectivity profile (Figure 1G and 1H) of the premotor module.

We also calculated global network efficiency, which quantifies the ease of information flow in the network and is computed as the inverse of the shortest path length between 2 nodes.²⁶

Statistical Analyses

We performed general linear regression analyses to determine the effect of fiber loss on verbal IQ, with verbal IQ as the dependent variable and whole-brain fiber density as the predictor variable. We also constructed a second model to adjust for key covariates with whole-brain fiber density, age, CCI, education, and physical activity (Community Healthy Activities Model Program for Seniors) predicting verbal IQ. We did not account for sex because the cohort was predominantly made up of women (80%).

For each subject's connectome, we extracted the global efficiency, modularity score, and the optimal community structure that indicates to which communities each ROI belongs. Due to stochasticity of network partitioning, which may lead to assignment of ROIs to different communities with every run, we performed 100 runs of modularity assessment function for each individual and used the mean as the modularity score. To determine differences in network topology, we performed a 2-tailed t test that compared the modularity scores of participants with versus those without cardiovascular risk factors. We also explored the community structure of 3 exemplar participants: 1 healthy control, a participant with only 1 cardiovascular risk factor, and 1 participant with all 3 cardiovascular risk factors. Finally, to determine the effect of fiber loss on network topology and efficiency, we performed Pearson correlation analyses between whole-brain fiber density and whole-brain modularity and global efficiency. All statistical analyses were performed using MATLAB (Mathworks, Natick, MA). The statistical significance was set at $P \leq 0.05$ (2-sided), and the P -values were Bonferroni corrected at $P \leq 0.05$.

Results

Participant Demographics

Table provides the descriptive statistics of the participants included in this study.

Relationship Between Connectome Density and Verbal IQ

Our model revealed that connectome density alone accounted for about 23% of the variance in predicting verbal IQ: $F(1,60)$

$= 18.7$, $P < 10^{-4}$, adjusted $R^2 = 0.23$. When age, years of education, cardiovascular risk factor burden, and level of physical activity were added, connectome density ($P = 0.004$), years of education ($P < 10^{-6}$), and CCI ($P = 0.05$) were significant predictors and accounted for about 60% of the variance in predicting verbal IQ: $F(5,60) = 18.2$, $P < 10^{-9}$, adjusted $R^2 = 0.59$. Physical activity ($P = 0.31$) and age ($P = 0.29$) were not significant predictors in the model.

Pearson correlations revealed that connectome density was significantly correlated with verbal IQ scores ($r = -0.49$, $P < 10^{-4}$; Figure 2A, left panel), such that subjects with densely connected networks performed better in the behavioral task, and subjects who had lost some fiber connections performed worse. The relationship was still significant even when we controlled for other significant predictors of verbal IQ: for example, years of education ($r = 0.45$, $P < 10^{-3}$) and CCI ($r = 0.42$, $P < 10^{-3}$). The models were still significant when corrected for multiple comparisons ($P = 0.025$).

Effect of Cardiovascular Risk Factors on Connectome Density and Long-Range White Matter Connectivity

There was decreased connectome density in participants with cardiovascular risk factors, and a significant difference was seen between participants with no cardiovascular risk factor and the cumulative morbidity group (Figure 2C, first panel: left hemisphere, $t[38] = 2.0470$, $P = 0.048$; right hemisphere, $t[38] = 2.1154$, $P = 0.041$).

Across all subjects, 54.4%, 40.1%, and 4.9% of all fibers were classified as short-, medium-, or long-range fibers, respectively. Subjects without cardiovascular risk factors had 54.3% short fibers, participants with at least 1 cardiovascular risk factor had 54.7% short fibers, and participants with cumulative morbidities had 58.3% short fibers. There was a significant difference in the number of short fibers between healthy controls and participants with cumulative morbidities ($P = 0.017$).

Subjects without cardiovascular risk factors had 40.3% medium fibers compared with 39.9% among participants with at least 1 cardiovascular risk factor and 37.6% among participants with cumulative morbidities. There was a significant difference in the number of medium fibers between healthy controls and participants with cumulative morbidity ($P = 0.015$).

Subjects without cardiovascular risk factors had 5.0% long fibers, whereas participants with at least 1 cardiovascular risk factor and participants with cumulative morbidities had 4.9% and 3.4% long fibers, respectively. There was a significant difference in the number of long fibers between healthy controls and participants with cumulative morbidity ($P = 0.028$).

These results indicate an overall loss of mid- and long-range connections due to multiple cardiovascular risk factors.

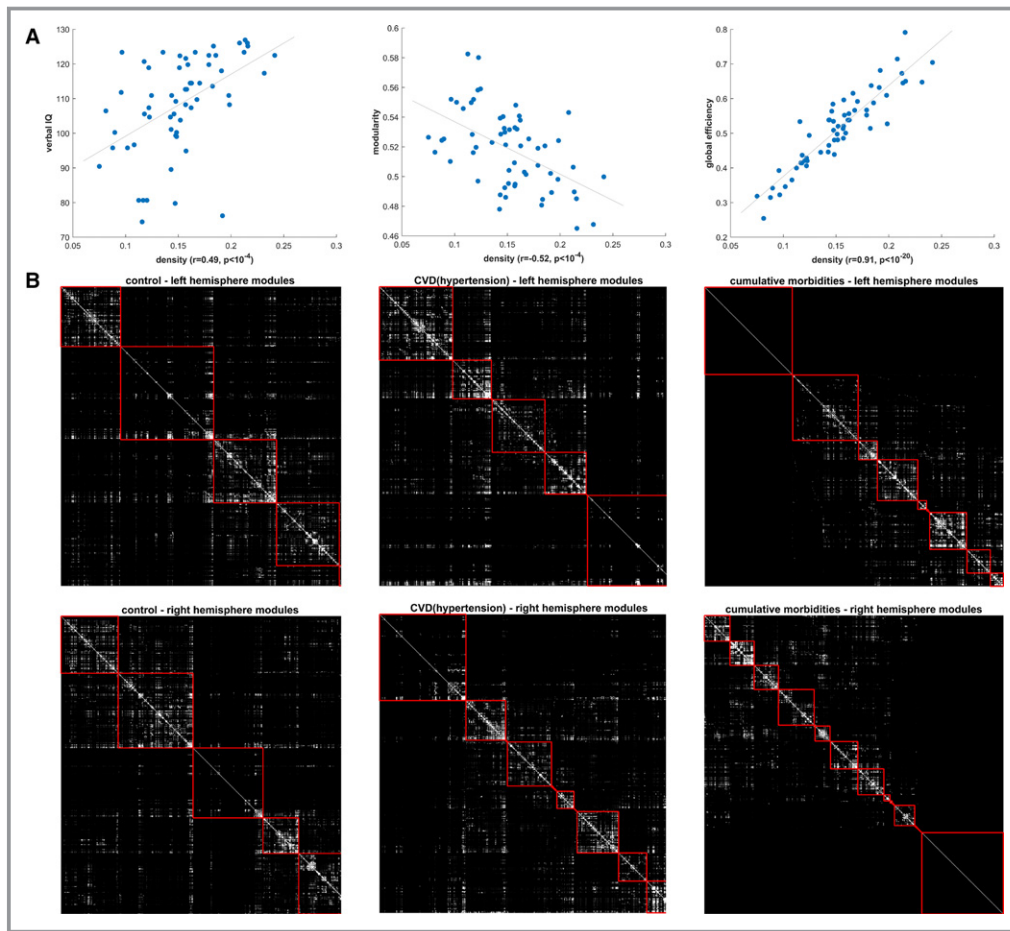


Figure 2. **A**, Left, Correlation between density and verbal IQ ($r=0.49$, $P<10^{-4}$). **A**, Middle, Correlation between density and modularity ($r=-0.52$, $P<10^{-4}$). **A**, Right, Correlation between density and global efficiency ($r=0.91$, $P<10^{-20}$). **B**, Sample data: number of modules detected in the left and right hemispheres of 1 healthy control, 1 participant with cardiovascular risk factors (hypertension), and 1 participant who had all cardiovascular risk factors (cumulative morbidities). Note the breakdown and increased number of modules (or fragmentation of the community structure) with increasing number of cardiovascular risk factors. Also note decreasing density with increasing cardiovascular risk factors, with the complete loss of connections in the participant with cumulative morbidities. **C**, Left, Effect of cardiovascular risk factors on density: decreasing left and right hemisphere density with increasing number of cardiovascular risk factors. Significant difference in density between controls and cumulative morbidity ($P=0.048$, $P=0.041$, respectively). **C**, Right, Effect of cardiovascular risk factors on modularity; increasing left and right hemisphere modularity with increasing number of cardiovascular risk factors. Significant difference in modularity between controls and cumulative morbidity ($P<10^{-3}$, $P=0.0028$, respectively). CVD indicates cardiovascular disease.

The results were significant when corrected for multiple comparisons ($P=0.02$).

Effect of Fiber Loss on Network Topology and Efficiency

There was a significant correlation between connectome density and modularity ($r=-0.52$, $P<10^{-4}$), and connectome density and global efficiency ($r=0.91$, $P<10^{-20}$) (Figure 2A, middle and right panels). Furthermore, examination of community structures revealed a fragmentation pattern in both hemispheres of

participants with cardiovascular risk factors. Figure 2B shows 3 example participants: 1 participant without cardiovascular risk factors, 1 participant with only 1 cardiovascular risk factor, and 1 participant with all 3 cardiovascular risk factors. There is a gradual decrease in the number of connections, or an increasing sparsity of the networks, and an increase in the number of modules (a fragmentation of the network) from the control on the left to the participant with cumulative morbidities on the right. Likewise, there was an increase in the left- and right-hemisphere modularity scores with increasing cardiovascular risk factor burden (left hemisphere, $t[38]=-3.6039$, $P<10^{-3}$; right hemisphere, $t[38]$

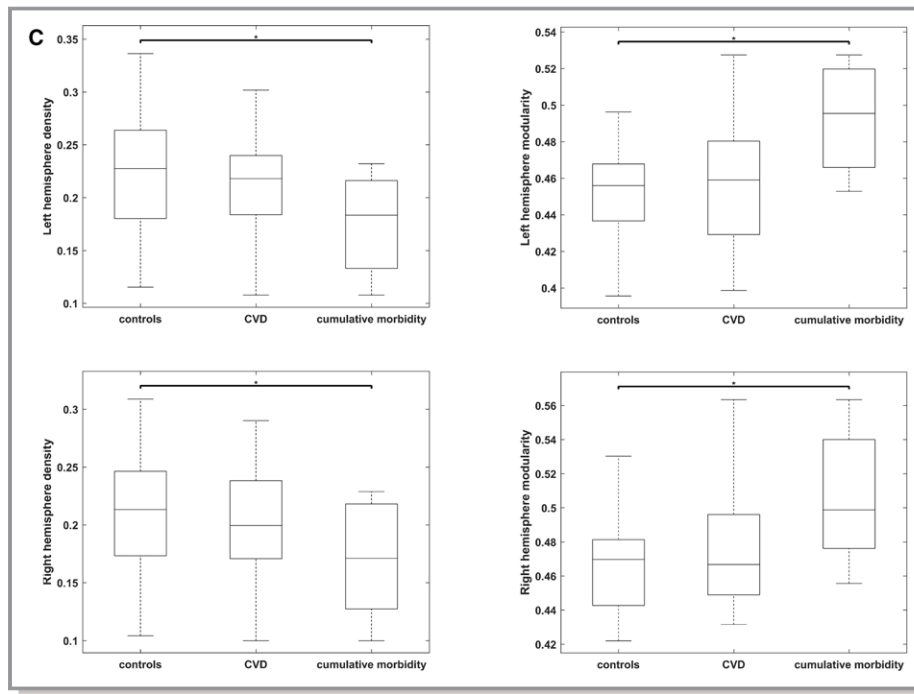


Figure 2. Continued

$=-3.2001$, $P=0.0028$; Figure 2C, second panel). The results were significant when corrected for multiple comparisons ($P=0.01$).

Discussion

We examined the relationships among cardiovascular risk factors, the integrity of axonal fibers, and verbal IQ using structural connectomes from a cohort of participants with various degrees of cardiovascular risk factors. Our results supported our hypothesis that a high cardiovascular risk factor burden would be associated with the loss of energy-dependent long axonal projections, leading to lower verbal IQ. This suggests that cardiovascular risk factor burden is associated with loss of longer-range white matter fibers, disruption of network architecture and efficiency, and lower cognitive performance. Network density alone predicted 23% of cognitive performance, and including sociodemographic and health variables increased the prediction accuracy to 60%. We found that participants with cardiovascular risk factors showed network disruption and a reduction in network density. We further demonstrated relationships among cardiovascular risk factors, brain integrity, and functional outcomes, indicating that white matter integrity is 1 potential approach to measure brain health because it is associated with both cardiovascular risk factor status and cognitive performance.

White matter is more vulnerable to injury caused by hypoperfusion than gray matter,²⁷ with lower collateral blood supply in the deep white matter. For this reason cardiovascular risk factors, particularly hypertension and diabetes mellitus,

lead to microangiopathic white matter injuries that are conspicuously observed on routine MRIs in individuals with cardiovascular risk factors or in the elderly. These are commonly referred to as cerebral small vessel disease (SVD)²⁸ and are directly associated with amyloid angiopathy, atherosclerosis, and arteriolosclerosis.²⁹ Cerebral SVD can be detected on routine MRIs by white matter hyperintensities (WMH), and their progressive accumulation has been shown to be associated with the development of low white matter and low brain volume, dementia, mood disturbances, and gait problems.³⁰ The Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Cohort study prospectively assessed 503 individuals with SVD and observed that a high WMH volume was associated with a hazard ratio of 1.8 for the development of parkinsonism, most commonly vascular parkinsonism.³¹ In the same cohort (503 subjects from the Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Cohort study), the investigators observed a 5.5-year cumulative risk of 11.1% of developing dementia, with white matter volume, WMH, and hippocampal volume explaining most of the variance.³² The same group also observed that SVD affecting frontosubcortical regions was more common in individuals with depressive symptoms.³³

Interestingly, the associations described above are well defined in cases of high or cumulative SVD burden, but in most cases, WMH are incidental findings on MRI, and their clinical significance is largely unknown.³⁰ They likely represent the early manifestation of an insidious process whose consequences remain subclinical until a threshold of structural compromise is reached. The ability to accurately detect these

changes in an early stage could lead to strategies to inform decisions about their significance, progression, and treatment. Diffusion MRI is a promising technique for this goal because ongoing technological developments have increased its sensitivity to small changes in tissue and white matter microstructure.³⁴ However, the findings from early studies were not able to definitely conclude whether they added benefit over the simple volume of WMH. For example, in the dementia study cited above, the authors concluded that tract-based spatial statistics, which is a form of quantification of scalar diffusion parameters along the core of white matter pathways, did not reveal additional benefit in predicting dementia.³² Similarly, the depression study did not observe an additional benefit of radial diffusivity after additional adjustment for WMH and lacunar infarcts.³³ Nonetheless, several more recent studies have started to disclose the important role of diffusion MRI in identifying subtle white matter changes in the context of SVD. As part of the PRESERVE (How Intensively Should We Treat Blood Pressure in Established Cerebral Small Vessel Disease?) DTI study, Croall and colleagues observed that after normalization for brain volume, WMH, lesion load, number of lacunae, and scalar diffusion measures such as fractional anisotropy and mean diffusivity were significantly associated with multiple cognitive domains such as verbal fluency, mental flexibility, and cognition.³⁵ Moonen and colleagues, as part of the DANTE (Discontinuation of Antihypertensive Treatment in Elderly People) Study Leiden, observed that lower fractional anisotropy in white matter was associated with executive functioning after adjustment for normalized brain volume, but diffusion measures were not associated with mood scores.³⁶ Ciulli and colleagues observed that a predictor model built on white matter mean diffusivity could forecast executive function (Trail Making Test performance) in patients with mild cognitive impairment and SVD with an accuracy of 77.5% to 80.0%.³⁷

It is important to emphasize that the more recent studies mentioned above were performed using scalar measures (ie, voxelwise metrics) of diffusion MRI, such as fractional anisotropy and mean diffusivity, whereas modeling of white matter networks and circuitry topology using diffusion tractography is the subsequent step to determine the complexity of brain networks. In a pilot study, Xie and colleagues demonstrated that depressive symptoms in patients with SVD were associated with impairment of global network efficiency and lower nodal efficiency in several brain regions.³⁸ More similarly to our approach, Tuladhar and colleagues demonstrated that SVD patients had less dense networks, with lower network strength and efficiency and with reduced connectivity between hub (rich club) regions.³⁹ This study did not test the relationship between white matter topology and cognitive symptoms but proposed their likely association.

Our study builds on the literature discussed above, combined with a risk factor determinant and functional

consequences to assess their tripartite association: cardiovascular risk factors ↔ white matter integrity ↔ functional performance.

We observed that cardiovascular risk factors were associated with reduced density. Connectome density gauges how well the network is connected and informs on the wiring or physical cost of connecting the network. Biological networks are sparsely connected, and only a fraction of possible connections occur. For instance, cortical fiber tract connectivity in mammalian brains is between 10% and 30%.⁴⁰ Density is dependent on the overall number of white matter projections, and we observed that cardiovascular risk factors were associated with a reduction in connectome density, that is, with white matter fiber loss in general with a disproportionate loss of longer connections. The human brain, even at rest, consumes about 20% of energy while making up only 2% of human weight. The energy consumed goes into generating action potentials, neurotransmitter release, and recycling; however, a large portion of the energy goes into maintaining resting potentials via active transport of ions across the membrane (about 28% for neurons).⁴¹ The cost of forming and maintaining these connections increases with increasing surface area, volume, length, and activity such that longer fibers are more costly, occupy more space, and generally require more energy. This suggests that to conserve energy and space, most connections in the brain should be short range (as supported by our analysis, 54.4% short-range fibers, 40.1% midrange fibers, and 4.9% long-range fibers). However, minimizing energy costs must also be balanced against maintaining an efficient topological organization that allows for efficient information processing and transfer. Therefore, the inherent segregation or increased connectivity within modules (that utilizes short-distance connections) must be accompanied by integration or communication between the modules (which utilizes long-distance connections) to allow for a globally efficient topology. We observed a significant loss of long-distance fibers in participants with cardiovascular risk factors, which led to a disruption of their topological organization and lowering of their overall network efficiency.

We posit that decreased connectome density, and the loss of long-distance fiber connections in particular, led to the observed fragmentation pattern and lowered efficiency of the white matter networks, which was in turn associated with lower verbal IQ. The association between density and verbal IQ remained significant even when potential confounders such as years of education and age were accounted for.

The topological organization of brain networks is thought to provide an insight into efficient cognitive processing of the brain, where high intramodular connectivity favors local processing and functional specialization, and connectivity between modules favors global integration.⁴² However, deviations from this optimal structure with either increased or decreased clustering may be the underlying cause or consequence of many cognitive and psychiatric disorders. Of note is

that we cannot determine causality because this was a single cross-sectional study; however, we observed that loss of long-range fiber connections resulting from cardiovascular risk factors was associated with deviations from this optimal topological architecture that signifies a healthy brain.

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Disclosures

None.

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