Title

Regional Vulnerability of the Corpus Callosum in the Context of Cardiovascular Risk

Journal

Journal of Geriatric Psychiatry and Neurology, 36(5)

ISSN

0891-9887

Authors

VandeBunte, Anna M

Fonseca, Corrina

Paolillo, Emily W

et al.

Publication Date

2023-09-01

DOI

10.1177/08919887231154931

Peer reviewed

HHS Public Access

Author manuscript

J Geriatr Psychiatry Neurol. Author manuscript; available in PMC 2023 September 01.

Published in final edited form as:

J Geriatr Psychiatry Neurol. 2023 September ; 36(5): 397–406. doi:10.1177/08919887231154931.

Regional Vulnerability of the Corpus Callosum in the Context of Cardiovascular Risk

Anna M. VandeBunte[1,2], **Corrina Fonseca**[1], **Emily W. Paolillo**[1], **Eva Gontrum**[1], **Shannon Y. Lee**[1], **Joel H. Kramer**[1], **Kaitlin B. Casaletto**[1]

[1]Department of Neurology, University of California, San Francisco, Memory and Aging Center, San Francisco, CA, USA

[2]Palo Alto University, CA, USA

Abstract

Many factors outside of cardiovascular health can impact the structure of white matter. Identification of reliable and clinically meaningful biomarkers of the neural effects of systemic and cardiovascular health are needed to refine etiologic predictions. We examined whether the corpus callosum demonstrates regional vulnerability to systemic cardiovascular risk factors. Three hundred and ninety-four older adults without dementia completed brain MRI, neurobehavioral evaluations, and blood draws. A subset (n = 126, n = 128) of individuals had blood plasma analyzed for inflammatory markers of interest (IL-6 and TNF-alpha). Considering diffusion tensor imaging (DTI) is a particularly reliable measure of white matter integrity, we utilized DTI to examine fractional anisotropy (FA) of anterior and posterior regions of the corpus callosum. Using multiple linear regression models, we simultaneously examined FA of the genu and the splenium to compare their associations with systemic and cardiovascular risk factors. Lower FA of the genu but not splenium was associated with greater systemic and cardiovascular risk, including higher systolic blood pressure (β = −0.17, p = .020), hemoglobin A1C (β = −0.21, p = .016) and IL-6 (β = −0.34, p = .005). FA of the genu was uniquely associated with cognitive processing speed (β = 0.20, p = .0015) and executive functioning (β = 0.15, p = .012), but not memory performances (β = 0.05, p = .357). Our results demonstrated differential vulnerability of the corpus callosum, such that frontal regions showed stronger, independent associations with biomarkers of systemic and cardiovascular health in comparison to posterior regions. Posterior white matter integrity may not reflect cardiovascular health. Clinically, these findings support the utility of examining the anterior corpus callosum as an indicator of cerebrovascular health.

Corresponding Author: Kaitlin B. Casaletto, ABPP-CN UCSF Memory and Aging Center, 675 Nelson Rising Lane, Suite 190, San Francisco, CA 94158, USA. Kaitlin.Casaletto@ucsf.edu.

Author Contributions

AV and KC contributed to the conception and design of the study. CF, SL, and EG were involved in data curation. AV and KC performed the statistical analysis. AV wrote the manuscript original draft. CF wrote the neuroimaging sections of the manuscript. EW assisted in original manuscript edits and figure composition. JK provided critical edits and study funding. All authors contributed to manuscript revision, read, and approved the submitted version.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Joel H. Kramer receives royalties from Pearson's Inc. The authors report no other conflict of interest.

Supplemental Material

Supplemental material for this article is available online.

Keywords

cerebrovascular; inflammatory markers; cognitive aging; diffusion tensor imaging; blood glucose; blood pressure

Introduction

Integrity of cerebral white matter is fundamental for brain health, and can be a sensitive biomarker of cognitive changes, even in typically aging older adults.[1,2] Several studies have shown a strong association between white matter integrity and age-related cognitive decline.[3,4] More specifically, declines in executive functioning, processing speed, and decision-making abilities have been associated with reduced integrity of the white matter in otherwise typically aging adults.[5–7] White matter integrity is also increasingly implicated in the development of dementia due to a range of etiologies.[8,9] In clinical practice, white matter injury (regardless of location) is often attributed systemic and cardiovascular health. Indeed, several studies do demonstrate associations between hypertension, elevated heart rate, and diabetes with "vascular dementia".[10–14] Metabolic (hemoglobin A1C) and inflammatory (IL-6 and TNF-alpha) biomarkers have also been closely associated with altered white matter integrity, demonstrating the importance of systemic cardiovascular factors for the health of cerebral white matter.[15–17] However, there is accumulating literature suggesting that white matter changes may reflect processes beyond an individual's cardiovascular health.

Indicators of white matter changes on brain MRI can reflect degeneration related to etiologies other than vascular disease. For instance, studies have demonstrated associations between Alzheimer's disease pathology and degree of white matter hyperintensities, such that greater white matter injury relates to increased beta-amyloid accumulation and tau deposition.[18–22] Additionally, degradation of white matter has been associated with frontotemporal lobar degeneration, highlighting involvement of white matter health in other neurodegenerative pathologies as well.[23]

Previous studies have also demonstrated some degree of regional specificity in cerebral white matter,[24] which is important in distinguishing the effects of cardiovascular disease from other progressive, neurogenerative diseases in older adults. For instance, greater white matter hyperintensities in frontal regions have been preferentially associated with cardiovascular disease.[25] Consequently, it is increasingly important to identify robust, *in-vivo* monitoring tools to aid in differentiating when white matter burden is reflective of systemic and cardiovascular health versus other more progressive disease pathologies.

The corpus callosum is an easily detected, large bundle of white matter that is considered a reliable MRI signal of white matter integrity.[26] In particular, diffusion tensor imaging (DTI) of the corpus callosum has demonstrated effectiveness in differentiating early-stage neurodegenerative processes from normal aging and has been associated with cognitive impairment.[27–30] DTI of the corpus callosum may be particularly sensitive to early white matter changes, considering it has been associated with cognition even in typically aging adults, whereas other imaging markers (i.e., white matter hyperintensities) may be more

reflective of end stage white matter disease.[22,31] These characteristics underscore the potential utility of using DTI of the corpus callosum as a clinically meaningful measure of the effects cardiovascular health on the brain.

In the current study, we aimed to examine whether the corpus callosum demonstrates specific regional vulnerability to systemic and cardiovascular risk in a large, carefully characterized cohort of older adults without dementia. Using fractional anisotropy (FA) and mean diffusivity (MD) measured via DTI as proxies for white matter integrity, we examined the independent relationships between the integrity of anterior (genu) versus posterior (splenium) regions of the corpus callosum as simultaneous predictors in the same model, against a panel of systemic and cardiovascular health indicators in a large cohort of older adults without dementia. A sample of older adults without dementia is ideal for assessing the utility of regional corpus callosum DTI metrics (such as FA and MD) to detect age-related changes related to cardiovascular health less impacted by overt neurodegenerative disease. Considering previously demonstrated associations between systemic vascular risk and white matter, we hypothesized that higher systolic blood pressure, hemoglobin A1C, resting heart rate, and inflammatory protein levels (IL-6, TNF-alpha) would relate to lower white matter integrity. Moreover, we hypothesized that greater systemic and cardiovascular risk would relate with decreased integrity of the genu independent of the integrity of the splenium.

Material and Methods

Participants

Three hundred and ninety-four older adults without dementia enrolled in the UCSF Memory and Aging Center's Longitudinal Brain Aging Study who completed diffusion tensor imaging, and a neurologic exam including vitals and clinical labs were included in the study (See Table 1). A subset also completed a blood draw with plasma analyzed for IL-6 and TNF-alpha ($n = 126$, $n = 128$, respectively). Inclusion criteria consisted of (1) no diagnosed memory or neurological conditions (e.g., Multiple Sclerosis, large vessel stroke), (2) no major medical conditions (e.g., heart disease, Diabetes Mellitus, HIV), (3) no DSM-5 major psychiatric disorders, (4) no active substance abuse and (5) minimal functional decline operationalized as Clinical Dementia Rating (CDR) of 0-0.5 via study partner interviews. On average participants were 69 years-old and 44% female, with minimal cardio- and cerebrovascular medical histories (2.53% with remote history of heart attack, stroke, or TIA; Table 1).

The study was approved by the institutional review board of the University of California, San Francisco and is conducted in accordance with the latest Declaration of Helsinki, including written informed consent from all participants.

Brain MRI

Magnetic Resonance Imaging (MRI) scans were performed at the UCSF Neuroscience Imaging Center using the 3T Magnetom TrioTIM Siemens Trio system (Siemens, Iselin, NJ, USA). All the data were collected in the sagittal plane. Before processing, all imaging data

were visually inspected for quality. Images with excessive motion or image artifact were excluded.

DTI Acquisition and Processing

Diffusion tensor imaging (DTI) data were acquired using the following parameters: TR/TE 8200/86 ms; B = 0 image and 64 directions at B = 2000 s/mm^2; FOV 220 × 220 mm^2 and 2.2 mm thick slices; matrix 100 × 100 with 60 slices yielding 2.2 mm^3 isotropic voxels. Diffusion images were processed using FSL[32] and Dipy[33] utilities. The diffusion direction images were co-registered to the b = 0 image using FSL MCFLIRT[34]. Background voxels not considered as brain tissue were then masked out of the diffusion volumes by applying a median Otsu function Gradient direction eddy current and distortion correction were applied to the realigned images. Diffusion tensors were fitted using Dipy[33] with a non-linear least-squares approach. Fractional anisotropy (FA) and mean diffusivity (MD) derived from the fitted tensor was reconstructed in the native space for quality control. A group template was created by registering all subjects' full tensor images to each other through iterative linear and non-linear registration algorithms using DTI-TK software.[35] By using the full tensor image of each subject, DTI-TK maximizes the alignment of white matter structures and minimizes interpolation of the diffusion images. Deformations were applied to bring each subject's FA and MD images to group template space and to the standard space atlas ICBM-DTI-81[36] to extract tracts of interest. For the present study, we chose the genu and splenium of the corpus callosum as our tracts of interest.

Systemic and Cardiovascular Risk Factors

Risk factors of interest included hemoglobin A1C, resting heart rate, hypertension, and plasma markers TNF-alpha and IL-6, given previously reported relationships between each of these factors and brain health.[37–40]

Hemoglobin A1C

Whole blood and serum samples were collected and stored in 0.5 mL aliquots at −80°C following baseline 12 h fasting blood draws, until used for biochemical processing. All laboratory analyses were performed by UCSF Clinical Laboratories, a CLIA-certified, CAP-accredited laboratory at UCSF Mission Bay Hospital. Hemoglobin A1C levels were determined from whole blood by means of an Abbott Architect c8000 enzymatic immunoassay.

Resting Heart Rate

Participant resting heart rates were measured by a clinician or study staff. A normal resting heart rate for adults ranges from 60-100 beats per minute.[41] Elevated heart rate is a risk factor for cardiovascular morbidity and mortality.[42]

Hypertension

Personal medical history, including presence of hypertension, was collected via self-report during the clinical interview with a neurologist. If the participant did not report a history of hypertension but indicated taking an antihypertensive drug, they were asked by the

clinician or study staff if they were prescribed the medication for their blood pressure. If the participant answered yes, they were considered to have a history of hypertension.

Plasma Inflammatory Markers

Blood was collected the morning after a 12-hour-fast and centrifuged at 2000×g for 15 minutes at 4°C. Plasma was transferred to 500 uL polypropylene cryovials for longterm storage at −80°C until analysis. Plasma was analyzed for IL-6 and TNF-alpha using the human proinflammatory panel 1 V-PLEX kit provided by Meso Scale Diagnostics, LLC (Rockville, MD), and scanned using the MESO QuickPlex SQ 120.

Cognitive Functioning

We utilized sample-based z-scores from several neuropsychological measures and averaged them together to create separate composite scores for each domain of cognitive functioning (i.e., memory, processing speed, executive functioning).

Episodic Memory

The memory composite score included sub tests from the California Verbal Learning Test–Second Edition (CVLT-II,[43]: total immediate recall of a 16-item list initially presented over five learning trials, long delayed free recall total (20-minute delay), and recognition discriminability (d'). Additionally, to assess nonverbal memory we included total recall (out of 17 details) of the Benson figure after a 10-minute delay.[44]

Processing Speed

We assessed processing speed through five computerized tests of reaction time[45] to different visual stimuli[45] (lines, dots, shapes, search, abstract matching 1, abstract matching 2). Each test involved a practice trial in which the participants had to perform at greater than 70% accuracy to continue to the real assessment. Higher z-scores indicate slower reaction times (e.g., worse performance).

Executive Functioning

The executive functioning composite included total number of items recalled (60") from the Stroop interference task,[46] number of digits recalled in backwards order (WAIS-IV Digit Span[47]), and total completion time (in seconds) for a modified version of the Trail Making Test, where participants serially alternated between numbers and letters.[44] In addition, the composite included a phonemic fluency task "D words" (total number of words that start with "D" in 60 seconds[44]) and design fluency, a measure in which participants had to generate as many visual patterns as possible in 60 seconds (D-KEFS[48] Condition 1[48]).

Statistical Analyses

All analyses were conducted using JMP16 statistical software. First, we examined the association among fractional anisotropy (FA) of the genu and FA of the splenium using a Spearman's rank correlation. Then we evaluated whether FA of the genu and/or splenium (simultaneously entered in the model) related to systemic and cardiovascular risk factors

of interest (i.e., systolic blood pressure, resting heart rate, hemoglobin A1C, TNF-alpha, and IL-6) via multiple linear regression models, covarying for age, sex, and education. We examined variance inflation factor (VIF) to assess multicollinearity in each of our regression models. Lastly, we examined the consistency of these associations by substituting in mean diffusivity of the genu and splenium instead of FA.

Given that we found an association between the genu and cardiovascular risk, we aimed to expand on these findings by exploring clinical correlates of the genu. Specifically, we evaluated associations between FA of the genu and several cognitive outcomes of interest (i.e., processing speed, executive functioning, memory) via multiple linear regression models, covarying for age, sex, and education.

Results

FA of the genu demonstrated an expected positive association with FA of the splenium ($r = 0.63$, $p < .0001$). Controlling for age, sex, and years of education, lower FA of the genu, but not splenium, was associated with greater systemic and cardiovascular risk (See Table 2). Specifically, higher systolic blood pressure and hemoglobin A1C were both related to lower FA of the genu, independent of FA of the splenium. In contrast, in the same model, higher systolic blood pressure significantly related to FA of the splenium, but in the opposite (positive) direction than FA of the genu. Higher concentrations of plasma inflammatory protein IL-6 were also associated with lower FA of the genu (See Figure 1). Interestingly, in each model, the splenium parameter evidenced *positive* though largely nonsignificant associations with cardiovascular risk factors, with the exception of systolic blood pressure. We examined VIF for all models to assess if multicollinearity may be contributing to findings and found all VIFs were in the acceptable range (VIFs < 2.5). Resting heart rate and TNF-alpha were not significantly associated with either the genu or splenium (See Figure 1; Table 2). Our findings were largely consistent when examining MD of the genu and splenium across all outcomes, showing significant associations of genu MD with IL-6 and hemoglobin A1C (See Figure 2).

Post Hoc Models

Post hoc analyses revealed a positive association between FA of the genu and performance on cognitive tests involving information processing and executive functioning (See Table 3). Lower FA of the genu was associated with a slower speed of information processing ($\beta = 0.20$, $p = .0015$) and poorer performance on executive functioning tasks ($\beta = 0.15$, $p = .012$). Lower FA of the genu was not strongly associated with performance on tasks involving memory ($\beta = 0.05$, $p = .357$). These relationships were consistent when examining MD of the genu across all outcomes.

Discussion

The current study aimed to determine whether there are regional differences in susceptibility of the corpus callosum to cardiovascular risk. Indeed, our results demonstrate differential vulnerability of the corpus callosum, such that the frontal regions (genu) show associations

with biomarkers of systemic and cardiovascular health above and beyond the effect of posterior portions of the corpus callosum (splenium). More specifically, higher blood pressure and blood sugar level correlated with greater disruption of frontal white matter microstructure, even after controlling for age, sex, and education. Interestingly, hemoglobin A1C significantly related to anterior white matter health even in a sample of individuals without diabetes, demonstrating possible sensitivity of this blood sugar metric to detect lower integrity in this brain region.

Inflammation was also associated with frontal white matter, such that higher concentrations of plasma inflammatory cytokine IL-6 related to worse integrity of white matter in the genu. Importantly, we found a dissociation such that each of these cardiovascular risk factors did not consistently meaningfully relate with posterior white matter integrity. Therefore, lower frontal white matter integrity in older adults appears to reflect cardiovascular health, while posterior white matter integrity may not. Taken together, white matter injury found on neuroimaging should not always be attributed cardiovascular disease or risk. While this study was not designed to examine the effect of other pathologies that are potentially more relevant to posterior white matter integrity (e.g., Alzheimer's pathology), our findings suggest there may be less of an impact of cardiovascular risk in this region. The association found between cardiovascular risk and white matter microstructure in the genu (but not the splenium) also has high clinical relevance as a potentially easily detected, specific indicator of cerebrovascular disease.

While the exact underlying mechanism(s) for increased frontal vulnerability are not yet completely clear. An increasing number of studies have demonstrated a disproportionate impact of vascular disease on frontal regions of the brain.[49,50] In individuals with cerebrovascular disease, white matter hyperintensities in the prefrontal cortex are found to be significantly higher in volume than other regions, suggesting this region may be generally more vulnerable to white matter injury often attributed to small vessel disease. Moreover, there is an extensive network of small blood vessels in subcortical regions, which makes them more susceptible to cerebrovascular injury.[51] Given the extensive connectivity between subcortical and frontal circuits, one hypothesis is that vascular damage in subcortical white matter may disrupt axons involved in regulation of frontal neuronal metabolism.[49] For instance, white matter lesions in subcortical regions have been preferentially associated with frontal cortical hypometabolism, which can lead to cell death.[52,53] Interestingly, other studies have found that regardless of location, white matter injury is specifically associated with functional disruption of frontal networks. For example, specific frontal lobe hypometabolism has been found to relate to both (1) cardiovascular risk in participants with extensive white matter lesions and lacunar infarcts, and (2) white matter lesions regardless of their location in the brain.[24,49,54,55] Further, whole brain cerebrovascular pathology uniquely correlates with cortical atrophy in frontal regions.[56–58] Taken together with our findings, systemic cardiovascular health may be most strongly linked to frontal circuitry, including metabolic regulation, cortical structure, and white matter integrity.

Our findings also highlight the utility of genu integrity as a measure reflecting the effects of cardiovascular disease in the brain, aligning closely with and extending on previous literature. For instance, Raghavan et al. and Vemuri et al. demonstrated that the anterior

portion of the corpus callosum is a useful marker for declines in cardiovascular health in adults with mild cognitive impairment and in prodromal disease.[59,60] We extend these findings by examining this association in a large cohort of adults without dementia, and through a wider scope of systemic (e.g., inflammatory cytokines) and vascular outcomes. The genu is a large, easily detected bundle of white matter and therefore may be particularly well positioned as a risk-stratification and/or prognostication tool. Our results add to the strong support for utilization of anterior diffusion tensor imaging metrics to track the impact of cardiovascular disease on brain aging in older adults. For instance, our results could be a useful guide for clinicians differentiating between cardiovascular disease and other neurodegenerative pathologies. Clinicians may have greater confidence in cerebrovascular disease pathology as a contributing factor to neurocognitive disorders if both frontal white matter changes and cardiovascular risk factors (e.g., hypertension, hyperlipidemia) are present.

Given that we found support for the genu as a correlate of systemic cardiovascular disease, we explored clinically meaningful correlates via cognition. Our results demonstrate that frontal white matter microstructure (genu) tracks with cognition, namely executive functioning and processing speed. Importantly, we did not find an association between frontal white matter integrity and memory performance, suggesting cognitive specificity of the genu. These findings on anterior diffusion tensor imaging add to existing literature on the association between white matter changes (i.e., white matter hyperintensities and lacunar infarcts) and worsened performance on tests of executive functions and psychomotor speed.[50,61] Moreover, our results align with extant literature that has demonstrated an association between dementia due to cerebrovascular disease and disproportionate declines in executive functioning and processing speed, greater than memory.[62–64]

Limitations

Our study is not without limitations. With an observational study design, it is difficult to determine whether the examined relationships between regions of the corpus callosum (genu and splenium) and cardiovascular risk are truly due to the impact of cardiovascular health on the brain or reflecting effects of a common parallel process (e.g., general metabolic changes with age). Our cohort's high educational attainment (83% had at least college level education) impacts the generalizability of our findings. Additionally, utilizing a longitudinal design for our study would have provided the opportunity to track whether there are changes in regional specificity of the corpus callosum over time. We also did not explore the effect of potentially confounding factors (e.g., Alzheimer's disease pathology) in these relationships, which may have influenced the unexpected relationship between the splenium and systolic blood pressure. Studies that combine white matter neuroimaging with Alzheimer's disease biomarkers are needed to disentangle effects of common age-related neuropathologies. Lastly, our study is limited by the lack of inclusion of other imaging markers of white matter integrity in our analyses, such as white matter hyperintensities (WMH). It is possible that WMH are a confounding variable in the associations between DTI metrics of the corpus callosum and the outcomes of interest. However, the corpus callosum is a large region of white matter and it may be more robust to differences in the white matter and WMH overall. Future studies should investigate multiple measures of white matter integrity to

better understand their impact on diffusion metrics and their relationship to cardiovascular health in a clinically normal population.

Conclusions

Our results highlight that not all white matter changes are necessarily linked to systemic cardiovascular etiology. Particularly when white matter injury involves posterior regions, other neuropathologies should be considered. Importantly, our study underscores the utility of DTI of the genu as a potential indicator of the neurologic effects of cardiovascular disease. Continued examination of the neuropathological correlates and processes underlying white matter integrity are needed to inform more precise diagnosis and intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like to thank the National Institute on Aging, the Alzheimer's Association, and the Larry L. Hillblom Foundation Network for funding this study. We would also like to thank the participants and family members involved.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the following NIH-NIA grants: K23AG058752 (PI: KBC), R01AG072475 (PI: KBC), R01AG032289 (PI JHK), and ADRC P30 AG062422 (PI Rabinovici). Our work was also supported by the Alzheimer's Association AARG-20-683875 (PI: KBC).

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

References

1. Bennett IJ, Greenia DE, Maillard P, et al. Age-related white matter integrity differences in oldest-old without dementia. Neurobiol Aging. 2017;56:108–114. [PubMed: 28527525]
2. Brickman AM, Siedlecki KL, Muraskin J, et al. White matter hyperintensities and cognition: Testing the reserve hypothesis. Neurobiol Aging. 2011;32(9):1588–1598. [PubMed: 19926168]
3. de Lange AMG, Bråthen ACS, Grydeland H, et al. White matter integrity as a marker for cognitive plasticity in aging. Neurobiol Aging. 2016;47:74–82. [PubMed: 27565301]
4. Tuladhar AM, Van Norden AGW, De Laat KF, et al. White matter integrity in small vessel disease is related to cognition. Neuroimage Clin. 2015;7:518–524. [PubMed: 25737960]
5. Fjell AM, Westlye LT, Amlien IK, Walhovd KB. Reduced white matter integrity is related to cognitive instability. Journal of Neuroscience. 2011;31(49):18060–18072. [PubMed: 22159119]
6. Qiu C, Fratiglioni L. A major role for cardiovascular burden in age-related cognitive decline. Nature Reviews Cardiology. 2015;12(5):267–277. [PubMed: 25583619]
7. Timpe JC, Rowe KC, Matsui J, Magnotta VA, Denburg NL. White matter integrity, as measured by diffusion tensor imaging, distinguishes between impaired and unimpaired older adult decision-makers: A preliminary investigation. J Cogn Psychol (Hove). 2011;23(6):760–767. [PubMed: 24976948]

8. Samieri C, Perier MC, Gaye B, et al. Association of cardiovascular health level in older age with cognitive decline and incident dementia. JAMA. 2018;320(7):657–664. [PubMed: 30140876]
9. Raman MR, Kantarci K, Murray ME, Jack CR, Vemuri P. Imaging markers of cerebrovascular pathologies: Pathophysiology, clinical presentation, and risk factors. Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring. 2016;5(1):5–14.
10. Ahtiluoto S, Polvikoski T, Peltonen M, et al. Diabetes, Alzheimer disease, and vascular dementia. Neurology. 2010;75(13):1195–1202. https://n.neurology.org/content/75/13/1195 [PubMed: 20739645]
11. Fuhrmann D, Nesbitt D, Shafto M, et al. Strong and specific associations between cardiovascular risk factors and white matter micro- and macrostructure in healthy aging. Neurobiol Aging. 2019;74:46–55. [PubMed: 30415127]
12. Lee AY. Vascular dementia. Chonnam Med J. 2011;47(2):66–71. Available at: 10.4068/cmj.2011.47.2.66 [PubMed: 22111063]
13. Power MC, Tingle J v., Reid RI, et al. Midlife and late-life vascular risk factors and white matter microstructural integrity: The atherosclerosis risk in communities neurocognitive study. J Am Heart Assoc. 2017;6(5), e005608. 10.1161/JAHA.117.005608 [PubMed: 28522676]
14. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. Lancet Neurol. 2005;4(8):487–499. http://www.thelancet.com/article/S1474442205701411/fulltext [PubMed: 16033691]
15. Bettcher BM, Watson CL, Walsh CM, et al. Interleukin-6, Age, and corpus callosum integrity. PLoS One. 2014;9(9):106521.
16. Repple J, Karliczek G, Meinert S, et al. Variation of HbA1c affects cognition and white matter microstructure in healthy, young adults. Mol Psychiatry. 2021;26(4):1399–1408. https://pubmed.ncbi.nlm.nih.gov/31467393/ [PubMed: 31467393]
17. Lim J, Sohn H, Kwon MS, Kim B. White matter alterations associated with pro-inflammatory cytokines in patients with major depressive disorder. Clinical Psychopharmacology and Neuroscience. 2021;19(3):449. [PubMed: 34294614]
18. Alber J, Alladi S, Bae HJ, et al. White matter hyperintensities in vascular contributions to cognitive impairment and dementia (VCID): Knowledge gaps and opportunities. Alzheimers Dement (N Y). 2019;5:107–117. [PubMed: 31011621]
19. Sweeney MD, Montagne A, Sagare AP, et al. Vascular dysfunction—The disregarded partner of Alzheimer's disease. Alzheimer's and Dementia. 2019;15(1):158–167.
20. Marnane M, Al-Jawadi OO, Mortazavi S, et al. Periventricular hyperintensities are associated with elevated cerebral amyloid. Neurology. 2016;86(6):535–543. [PubMed: 26747881]
21. Dadar M, Manera AL, Ducharme S, Collins DL. White matter hyperintensities are associated with grey matter atrophy and cognitive decline in Alzheimer's disease and frontotemporal dementia. Neurobiol Aging. 2022;111:54–63. [PubMed: 34968832]
22. Lee S, Viqar F, Zimmerman ME, et al. White matter hyperintensities are a core feature of Alzheimer's disease: Evidence from the dominantly inherited Alzheimer network. Ann Neurol. 2016;79(6):929–939. [PubMed: 27016429]
23. Elahi FM, Marx G, Cobigo Y, et al. Longitudinal white matter change in frontotemporal dementia subtypes and sporadic late onset Alzheimer's disease. Neuroimage Clin. 2017;16:595–603. [PubMed: 28975068]
24. Gootjes L, Teipel SJ, Zebuhr Y, et al. Regional distribution of white matter hyperintensities in vascular dementia, Alzheimer's disease and healthy aging. Dement Geriatr Cogn Disord. 2004;18(2):180–188. [PubMed: 15211074]
25. Kim JH, Hwang KJ, Kim JH, Lee YH, Rhee HY, Park KC. Regional white matter hyperintensities in normal aging, single domain amnestic mild cognitive impairment, and mild Alzheimer's disease. Journal of Clinical Neuroscience. 2011;18(8):1101–1106. [PubMed: 21723730]
26. Lee DY, Fletcher E, Martinez O, et al. Vascular and degenerative processes differentially affect regional inter-hemispheric connections in normal aging, mild cognitive impairment, and Alzheimer disease. Stroke. 2010;41(8):1791–1797. [PubMed: 20595668]

27. Croall ID, Lohner V, Moynihan B, et al. Using DTI to assess white matter microstructure in cerebral small vessel disease (SVD) in multicentre studies. Clin Sci (Lond). 2017;131(12):1361–1373. [PubMed: 28487471]
28. Fu JL, Zhang T, Chang C, Zhang YZ, Li WB. The value of diffusion tensor imaging in the differential diagnosis of subcortical ischemic vascular dementia and Alzheimer's disease in patients with only mild white matter alterations on T2-weighted images. Acta Radiol. 2012;53(3):312–317. [PubMed: 22416261]
29. Sugihara S, Kinoshita T, Matsusue E, Fujii S, Ogawa T. Usefulness of diffusion tensor imaging of white matter in Alzheimer disease and vascular dementia. Acta radiol. 2004;45(6):658–663. [PubMed: 15587425]
30. Tu MC, Lo CP, Huang CF, et al. Effectiveness of diffusion tensor imaging in differentiating early-stage subcortical ischemic vascular disease, Alzheimer's disease and normal ageing. PLoS One. 2017;12(4):e0175143. [PubMed: 28388630]
31. Pietrasik W, Cribben I, Olsen F, Huang Y, Malykhin NV. Diffusion tensor imaging of the corpus callosum in healthy aging: Investigating higher order polynomial regression modelling. Neuroimage. 2020;213:116675. [PubMed: 32112960]
32. Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM. FSL. Neuroimage. 2012;62(2):782–790. https://pubmed.ncbi.nlm.nih.gov/21979382/ [PubMed: 21979382]
33. Garyfallidis E, Brett M, Amirbekian B, et al. Dipy, a library for the analysis of diffusion MRI data. Front Neuroinform. 2014;8(FEB):8. [PubMed: 24600385]
34. Otsu N Threshold selection method from gray-level histograms. IEEE Trans Syst Man CybernSMC. 1979;9(1):62–66.
35. Zhang H, Yushkevich PA, Rueckert D, Gee JC. Unbiased white matter atlas construction using diffusion tensor images. Med Image Comput Comput Assist Interv. 2007;10(Pt 2):211–218. https://pubmed.ncbi.nlm.nih.gov/18044571/ [PubMed: 18044571]
36. Mori S, Oishi K, Jiang H, et al. Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. Neuroimage. 2008;40(2):570–582. https://pubmed.ncbi.nlm.nih.gov/18255316/ [PubMed: 18255316]
37. Jayaraj RL, Azimullah S, Beiram R. Diabetes as a risk factor for Alzheimer's disease in the Middle East and its shared pathological mediators. Saudi J Biol Sci. 2020;27(2):736–750. [PubMed: 32210695]
38. Mahinrad S, Sorond FA, Gorelick PB. Hypertension and cognitive dysfunction: a review of mechanisms, life-course observational studies and clinical trial results. Rev Cardiovasc Med. 2021;22(4):1429–1449. 10.31083/j.rcm2204148/htm [PubMed: 34957783]
39. Wang WY, Tan MS, Yu JT, Tan L. Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease. Ann Transl Med. 2015;3(10):7–7. https://atm.amegroups.com/article/view/6546/7583 [PubMed: 25705639]
40. Imahori Y, Vetrano DL, Xia X, et al. Association of resting heart rate with cognitive decline and dementia in older adults: A population-based cohort study. Alzheimer's and Dementia. 2021;18(10):1779–1787. 10.1002/alz.12495
41. All About Heart Rate (Pulse) | American Heart Association. https://www.heart.org/en/health-topics/high-blood-pressure/the-facts-about-high-blood-pressure/all-about-heart-rate-pulse
42. Fox K, Borer JS, Camm AJ, et al. Resting heart rate in cardiovascular disease. J Am Coll Cardiol. 2007;50(9):823–830. [PubMed: 17719466]
43. Delis DC, Kramer JH, Kaplan E, Ober BA. CVLT-II California verbal learning test manual adult version. San Antonio, TX: Psychological Corporation; 2000.
44. Kramer JH, Jurik J, Sha SJ, et al. Distinctive neuropsychological patterns in frontotemporal dementia, semantic dementia, and Alzheimer disease. Cognitive and Behavioral Neurology. 2003;16(4):211–218. [PubMed: 14665820]
45. Kerchner GA, Racine CA, Hale S, et al. Cognitive processing speed in older adults: Relationship with white matter integrity. PLoS One. 2012;7(11):e50425. [PubMed: 23185621]
46. Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol. 1935;18(6):643–662.
47. Wechsler D WAIS-IV technical and interpretive manual. 4th ed. San Antonio Tex: Pearson; 2008.

48. Delis DC, Kaplan E, Kramer JH. Delis-Kaplan executive function system: Technical manual. San Antonio, TX: The Psychological Corporation;2001.
49. Tullberg M, Fletcher E, DeCarli C, et al. White matter lesions impair frontal lobe function regardless of their location. Neurology. 2004;63(2):246–253. [PubMed: 15277616]
50. Knopman DS, Griswold ME, Lirette ST, et al. Vascular imaging abnormalities and cognition: Mediation by cortical volume in non-demented persons: ARIC-NCS study. Stroke. 2015;46(2):433–440. [PubMed: 25563642]
51. Kalaria RN, Erkinjuntti T. Small vessel disease and subcortical vascular dementia. J Clin Neurol. 2006;2(1):1. [PubMed: 20396480]
52. Baron JC, D'antona R, Pantano P, Serdaru M, Samson Y, Bousser MG. Effects of thalamic stroke on energy metabolism of the cerebral cortex. A positron tomography study in man. Brain. 1986;109(Pt 66):1243–1259. [PubMed: 3491655]
53. Pappata S, Mazoyer B, Dinh ST, Cambon H, Levasseur M, Baron JC. Effects of capsular or thalamic stroke on metabolism in the cortex and cerebellum: A positron tomography study. Stroke. 1990;21(4):519–524. [PubMed: 2326833]
54. Moody DM, Bell MA, Challa VR. Features of the cerebral vascular pattern that predict vulnerability to perfusion or oxygenation deficiency: an anatomic study. AJNR Am J Neuroradiol. 1990;11(3):431. [PubMed: 2112304]
55. Kuczynski B, Jagust W, Chui HC, Reed B. An inverse association of cardiovascular risk and frontal lobe glucose metabolism; 2009.
56. Jagust WJ, Zheng L, Harvey DJ, et al. Neuropathological basis of magnetic resonance images in aging and dementia. Ann Neurol. 2008;63(1):72–80. https://pubmed.ncbi.nlm.nih.gov/18157909/ [PubMed: 18157909]
57. Reed BR, Eberling JL, Mungas D, Weiner M, Kramer JH, Jagust WJ. Effects of white matter lesions and lacunes on cortical function. Arch Neurol. 2004;61(10):1545–1550. https://jamanetwork.com/journals/jamaneurology/fullarticle/786864 [PubMed: 15477508]
58. Raji CA, Lopez OL, Kuller LH, et al. White matter lesions and brain gray matter volume in cognitively normal elders. Neurobiol Aging. 2012;33(4):834.
59. Raghavan S, Przybelski SA, Reid RI, et al. Reduced fractional anisotropy of the genu of the corpus callosum as a cerebrovascular disease marker and predictor of longitudinal cognition in MCI. Neurobiol Aging. 2020;96:176–183. [PubMed: 33022474]
60. Vemuri P, Lesnick TG, Przybelski SA, et al. Development of a cerebrovascular magnetic resonance imaging biomarker for cognitive aging. Ann Neurol. 2018;84(5):705–716. 10.1002/ana.25346 [PubMed: 30264411]
61. O'Brien JT, Wiseman R, Burton EJ, et al. Cognitive associations of subcortical white matter lesions in older people. Ann N Y Acad Sci. 2002;977:436–444. [PubMed: 12480784]
62. Kalaria RN. Neuropathological diagnosis of vascular cognitive impairment and vascular dementia with implications for Alzheimer's disease. Acta Neuropathol. 2016;3:659–685.
63. Song R, Xu H, Dintica CS, et al. Associations between cardiovascular risk, structural brain changes, and cognitive decline. J Am Coll Cardiol. 2020;75(20):2525–2534. [PubMed: 32439001]
64. Sachdev P, Professor S, Professor D, et al. Diagnostic criteria for vascular cognitive disorders: A VASCOG statement. Alzheimer Dis Assoc Disord. 2014;28(3):206–218. [PubMed: 24632990]

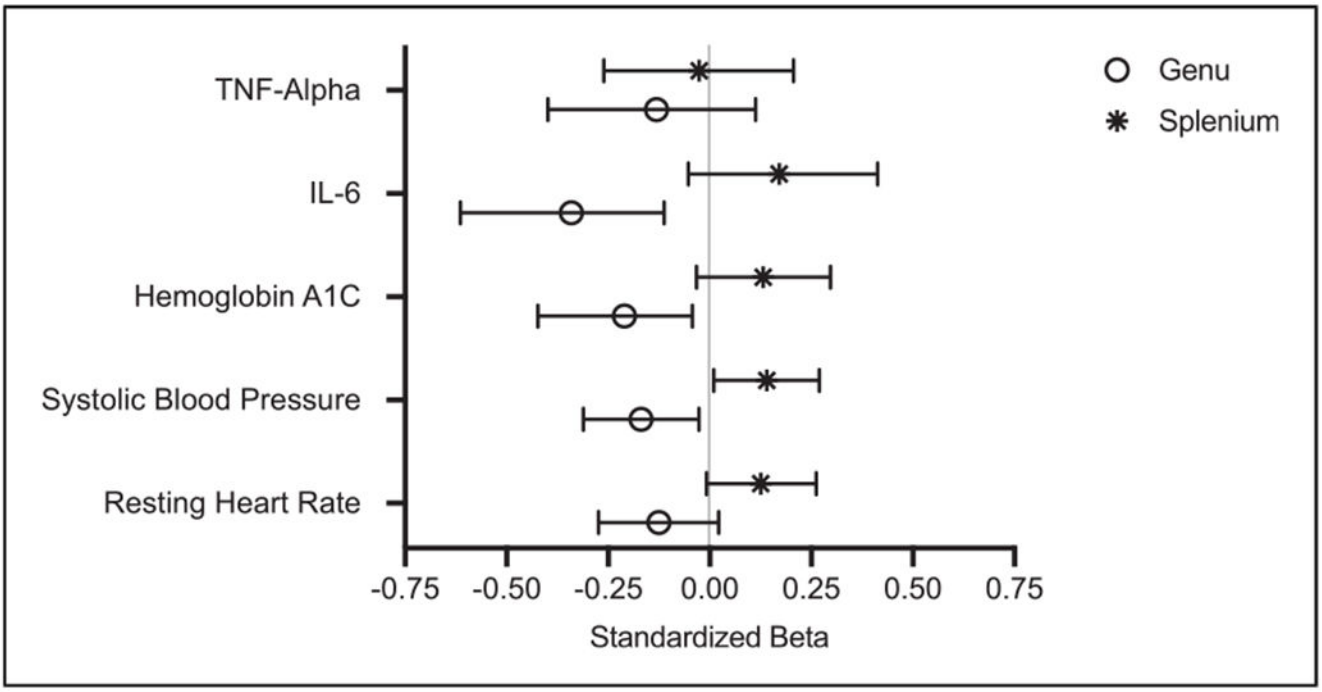

Figure 1.
Fractional anisotropy (FA) of genu but not splenium relates to systemic and cardiovascular risk factors. Note. Error bars represent 95% confidence intervals.

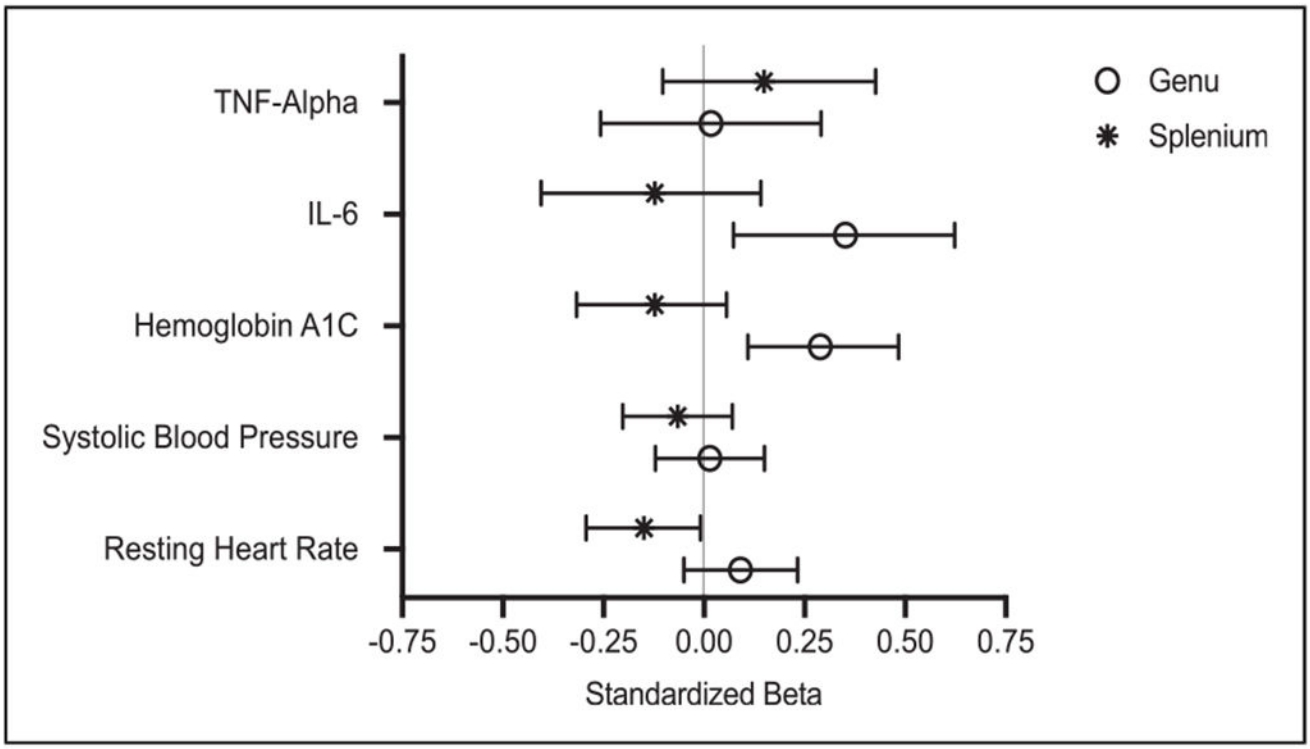

Figure 2.
Mean diffusivity (MD) of genu but not the splenium relates to systemic and cardiovascular risk factors. Note. Error bars represent 95% confidence intervals.

Table 1.

Study Sample Demographic and Clinical Characteristics.

	n	%(*n*) or *M*(*SD*)
Sex, % Female	394	43.79% (173)
Race	394	
White		83.64% (317)
Black		<1.00% (1)
Asian		15.03% (57)
Other		1.06% (4)
Age (years)	394	69.53(9.91)
Education (years)	394	17.23(2.30)
Cardiovascular Risk		
Systolic Blood Pressure	394	132.62(17.09)
Hemoglobin AIC	233	5.56(0.44)
Resting Heart Rate	388	67.29(10.62)
IL-6	126	1.01(1.22)
TNF-Alpha	128	2.59(1.49)

Note: *N* = 394. *n* = sample size available for each demographic or clinical characteristic. *M* = mean, *SD* = standard deviation.

Table 2.

Multiple Linear Regression Models Examining the Relationship Between Anterior and Posterior Corpus Callosum With Cardiovascular Risk Factors.

	Systolic Blood Pressure		Hemoglobin AIC		Resting Heart Rate		IL-6		TNF-Alpha	
	Std, B (95% CI)	p-value (DF: 5, 393)	Std, B (95% CI)	p-value (DF: 5, 232)	Std, B (95% CI)	p-value (DF: 5, 386)	Std, B (95% CI)	p-value (DF: 5, 125)	Std, B (95% CI)	p-value (DF: 5, 127)
Age	0.17 (0.006, 0.003)	0.003	0.005 (−0.02, 0.02)	0.943	−0.02 (−0.01, 0.01)	0.718	0.06 (−0.02, 0.04)	0.496	0.22 (0.006, 0.07)	0.019
Education	−0.21 (−0.13, −0.05)	<0.0001	0.01 (−0.05, 0.07)	0.854	−0.12 (−0.09, −0.007)	0.023	−0.06 (−0.1 1, 0.06)	0.531	−0.06 (−0.1 1, 0.05)	0.511
Sex	0.06 (−0.04, 0.16)	0.236	−0.02 (−0.15, 0.12)	0.821	−0.12 (−0.22, −0.02)	0.022	−0.01 (−0.19, 0.16)	0.886	−0.01 (−0.18, 0.16)	0.909
FA of the Genu	−0.17 (−0.31, −0.03)	0.020	−0.21 (−0.42, −0.04)	0.016	−0.13 (−0.27, 0.02)	0.097	−0.34 (−0.61, −0.11)	0.005	−0.13 (−0.40, 0.11)	0.272
FA of the Splenium	0.14 (0.01, 0.27)	0.035	0.13 (−0.03, 0.30)	0.117	0.13 (−0.009, 0.26)	0.067	0.17 (−0.05, 0.41)	0.130	−0.03 (−0.26, 0.21)	0.817

Note: Std, B = values represent standardized beta values; FA = Fractional Anisotropy, DF = degrees of freedom.

Table 3.

Multiple Linear Regression Post Hoc Analyses Examining the Relationship Between Anterior Corpus Callosum and Cognitive Outcomes.

	Information Processing Speed		Memory		Executive Functioning	
	Std, B	**p-value (DF: 4, 255)**	**Std, B**	**p-value (DF: 4, 313)**	**Std, B**	**p-value (DF: 4, 351)**
Age	0.26	<0.0001	−0.21	0.0004	−0.23	0.0001
Sex	0.02	0.772	0.28	<0.0001	0.03	0.576
Education	−0.07	0.264	0.15	0.005	0.22	<0.0001
FA of the Genu	−0.20	0.0015	0.05	0.357	0.15	0.012

Note: Std, B = values represent standardized beta values; FA = Fractional Anisotropy, DF = degrees of freedom.