Hypertension

ORIGINAL ARTICLE

Hypertensive Adults Exhibit Lower Myelin Content: A Multicomponent Relaxometry and Diffusion Magnetic Resonance Imaging Study

John P. Laporte, Mary E. Faulkner, Zhaoyuan Gong, Mohammad A.B.S. Akhonda, Luigi Ferrucci, Josephine M. Egan, Mustapha Bouhrara

BACKGROUND: It is unknown whether hypertension plays any role in cerebral myelination. To fill this knowledge gap, we studied 90 cognitively unimpaired adults, age range 40 to 94 years, who are participants in the Baltimore Longitudinal Study of Aging and the Genetic and Epigenetic Signatures of Translational Aging Laboratory Testing to look for potential associations between hypertension and cerebral myelin content across 14 white matter brain regions.

METHODS: Myelin content was probed using our advanced multicomponent magnetic resonance relaxometry method of myelin water fraction, a direct and specific magnetic resonance imaging measure of myelin content, and longitudinal and transverse relaxation rates (*R1* and *R2*), 2 highly sensitive magnetic resonance imaging metrics of myelin content. We also applied diffusion tensor imaging magnetic resonance imaging to measure fractional anisotropy, mean diffusivity, radial diffusivity, and axial diffusivity values, which are metrics of cerebral microstructural tissue integrity, to provide context with previous magnetic resonance imaging findings.

RESULTS: After adjustment of age, sex, systolic blood pressure, smoking status, diabetes status, and cholesterol level, our results indicated that participants with hypertension exhibited lower myelin water fraction, fractional anisotropy, *R1* and *R2* values and higher mean diffusivity, radial diffusivity, and axial diffusivity values, indicating lower myelin content and higher impairment to the brain microstructure. These associations were significant across several white matter regions, particularly in the corpus callosum, fronto-occipital fasciculus, temporal lobes, internal capsules, and corona radiata.

CONCLUSIONS: These original findings suggest a direct association between myelin content and hypertension and form the basis for further investigations including longitudinal assessments of this relationship. ***(Hypertension.* 2023;80:1728–1738. DOI: 10.1161/HYPERTENSIONAHA.123.21012.)** • **Supplement Material**.

Key Words: diffusion tensor imaging ■ hypertension ■ magnetic resonance imaging ■ myelin water fraction ■ neurodegeneration

Hypertension is the primary risk factor for stroke, ischemic white matter lesions, infarcts, and atherosclerosis, as well as cardiovascular and microvascular diseases.[1–3] Further, hypertension is the most widely accepted risk factor associated with a myriad of neurodegenerative diseases, especially Alzheimer's disease and related dementias.[4] Emerging evidence suggests that hypertension leads to vessel wall remodeling, potentially leading to hypoperfusion and associated hypoxia, as well as reduced glucose transport into the brain with concomitant accelerated cerebral tissue degeneration.[5,6] Indeed, this paradigm is further supported by recent longitudinal studies revealing a direct association between hypertension in midlife and reduced cerebral blood flow

Correspondence to: Mustapha Bouhrara, Magnetic Resonance Physics of Aging and Dementia Unit, Laboratory of Clinical Investigation, National Institute on Aging (NIA), NIH, BRC 05C-222, 251 Bayview Blvd, Baltimore 21224, MD. Email bouhraram@mail.nih.gov
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NOVELTY AND RELEVANCE

What Is New?

This is the first study, to our knowledge, that explicitly investigated the association between hypertension and cerebral myelin content probed using a direct magnetic resonance imaging measure.

What Is Relevant?

In a healthy adult population, elevated blood pressure is associated with reduced cerebral white matter tissue myelination. Further, patients under hypertension control medication still exhibit significantly lower myelin content as compared with control.

Clinical/Pathophysiological Implications?

This work lay the ground to future efforts to support myelin health in hypertension and examine the effect of hypertensive medications on mitigating myelin damage.

Nonstandard Abbreviations and Acronyms

AxD	axial diffusivity
bSSFP	balanced steady-state free precession
DAM	double angle method
DTI	diffusion tensor imaging
FA	fractional anisotropy
FSL	The FMRIB Software Library
MD	mean diffusivity
MRI	magnetic resonance imaging
MWF	myelin water fraction
R1	longitudinal relaxation rate
R2	transverse relaxation rate
RD	radial diffusivity
ROI	regions of interest
SPGR	spoiled gradient-recalled echo
TE	echo time
TR	repetition time

in later life.[7,8] Therefore, examining the extent of any possible association between hypertension and cerebral tissue integrity is paramount for our global understanding of neurodegenerative disease risk factors and progression.

In recent years, magnetic resonance imaging (MRI) studies, based extensively on diffusion tensor imaging (DTI), have revealed an association between hypertension and abnormal cerebral microstructural white matter integrity.[8] DTI is an MRI technique sensitive to the underlying microarchitecture of the brain parenchyma and the degree and direction of water molecule mobility. These studies have documented that hypertension, indicated by a blood pressure >140/90 mm Hg or the use of antihypertensive medication, is associated with lower values of fractional anisotropy (FA) and higher values of mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AxD).[9–11] Reduced FA concomitant with an increase in RD is associated with demyelination,[12] whereas reduced FA in conjunction with increased AxD is believed to be associated with axonal injury or death.[13] These changes in cerebral microstructural integrity associated with hypertension have been interpreted as deterioration in axonal myelination. However, although DTI metrics such as FA and MD are sensitive to cerebral microstructural changes, they are not specific. Indeed, there are multiple methodological and biological factors that can affect the DTI-derived eigenvalues from which the DTI indices are calculated[14,15]; these include, but not limited to, axonal degeneration, flow, temperature, hydration, macromolecular content and architectural features, including fiber fanning or crossing. Therefore, to our knowledge, the association between hypertension and myelination has not yet been established. To address this limitation, multicomponent relaxometry methods provide a greater specificity to quantify myelin content in white matter and probe related changes that occur during brain development and neurodegenerative diseases.[16,17] Multicomponent relaxometry separates the measured MR signal in white matter into 2 pools of water, namely the intra- and extracellular water pool and the water trapped between the myelin sheaths calculated as the myelin water fraction (MWF).[18,19] MWF is an in vivo specific index of myelin content and is a potential marker for myelin alterations. To the best of our knowledge, no MR studies have employed multicomponent relaxometry analysis, specifically MWF imaging, to investigate the relationship between myelin content and hypertension in aging adults.

In this study, we examined the association between hypertension and myelin content as probed using MWF on a cohort of well-characterized cognitively unimpaired adults (N=90), across the age range of 40 to 94 years. Each participant underwent our Bayesian Monte Carlo-mcDESPOT protocol for MWF as a direct measure of myelin content, as well as mapping of longitudinal and transverse relaxation rates (*R1* and *R2*) as sensitive but nonspecific measures of myelin content.[6,20–22] Indeed, *R1* and *R2* values depend on both water mobility and macromolecular tissue composition, including local lipid and iron content, the main constituents of myelin, and thus are expected to be directly associated with differences in

myelin content. To establish a connection with previous MRI findings, participants have undergone our additional DTI protocol for FA, MD, RD, and AxD mapping as well.[23]

METHODS

Data Availability

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

Study Cohort

Participants are volunteers of the Baltimore Longitudinal Study of Aging (BLSA) and the Genetic and Epigenetic Signatures of Translational Aging Laboratory Testing (GESTALT) studies.[24,25] Both BLSA and GESTALT seek to evaluate multiple biomarkers associated with aging, with essentially identical inclusion and exclusion criteria. Participants with metallic implants or major neurological or medical disorders are excluded on first admission. All participants were administered the Mini Mental State Examination (MMSE). Informed consent was obtained from participants before the conduct of the experiments, in compliance with the local Institutional Review Board.

Data Acquisition

MRI scans were performed on a 3T whole body Philips MRI system (Achieva, Best, The Netherlands) using the internal quadrature body coil for transmission and an 8-channel phased-array head coil for reception. Each participant underwent our Bayesian Monte Carlo-mcDESPOT protocol for MWF, *R1*, and *R2* mapping.[6,16,26,27] This imaging protocol consisted of 3D spoiled gradient-recalled echo (SPGR) images acquired with flip angles of (2 4 6 8 10 12 14 16 18 20)°, echo time (TE) of 1.37 ms, repetition time (TR) of 5 ms and acquisition time of ~5 minutes, as well as 3D balanced steady-state free precession (bSSFP) images acquired with flip angles of [2 4 7 11 16 24 32 40 50 60]°, TE of 2.8 ms, TR of 5.8 ms, and acquisition time of ~6 minutes. The bSSFP images were acquired with radiofrequency excitation pulse phase increments of 0 or 180° to account for off-resonance effects, with a total scan time of ~12 minutes (~6 minutes for each phase-cycling scan). All SPGR and bSSFP images were acquired with an acquisition matrix of 150×130×94, voxel size 1.6×1.6×1.6 mm. To correct for excitation radiofrequency inhomogeneity,[28,29] we used the double-angle method (DAM), which consisted of acquiring 2 fast spin-echo images with flip angles of 45° and 90°, TE of 102 ms, TR of 3000 ms, acquisition voxel size of 2.6×2.6×4 mm, and acquisition time of ~4 minutes. The total acquisition time was ~21 minutes. All images were acquired with field-of-view of 240×208×150 mm, SENSE factor of 2, and reconstructed to a voxel size of 1×1×1 mm. We emphasize that all MRI studies and ancillary measurements were performed with the same MRI system, with the same pulse sequences, and at the same facility for both BLSA and GESTALT participants.

The DTI protocol consisted of diffusion-weighted images (DWIs) acquired with single-shot EPI, TR of 10 s, TE of 70 ms, 2 *b*-values of 0 and 700 s/mm^2, with the latter encoded in 32 directions, acquisition matrix of 120×104×75, and acquisition voxel size of 2×2×2 mm. Two images at *b*=0 s/mm^2 were acquired and then averaged. All images were acquired with field-of-view of 240×208×150 mm.

Data Processing

For each participant, using the FLIRT analysis as implemented in the The FMRIB Software Library (FSL) software,[30] all SPGR, bSSFP, or DAM images were linearly registered to the SPGR image obtained at FA of 8° and the respective derived transformation matrices were then applied to the original SPGR, bSSFP, or DAM images. Then, a whole-brain MWF map was generated using Bayesian Monte Carlo-mcDESPOT from these co-registered SPGR, bSSFP, and DAM datasets.[6,16,20] Bayesian Monte Carlo-mcDESPOT assumes a 2-relaxation time components system consisting of a short component, attributed to myelin water, and a long component, attributed to intra- and extracellular water. We used the signal model explicitly accounting for nonzero TE.[6,16,20] This emerging method offers rapid and reliable whole-brain MWF map within feasible clinical time[6,16,20,31–34] and has been used in assessing myelin loss in mild cognitive impairment and dementias, as well as examining factors influencing cerebral myelination in normative aging.[16,22,23,26,32–45] A whole-brain *R1* map was also generated from the co-registered SPGR and DAM datasets using DESPOT1,[21] and a whole-brain *R2* map was generated from the co-registered bSSFP and DAM datasets using DESPOT2.[21] The DW images were corrected for eddy current using the function *eddy* in FSL and for motion effects using the affine registration tools as implemented in FSL[30] and registered to the DW image obtained with *b*=0 s/mm^2 using FNIRT. We used the DTIfit tool implemented in FSL to calculate the eigenvalue maps, which were used to calculate FA, RD, MD, and AxD.[46]

Further, using FSL software,[30] the averaged SPGR image over flip angles underwent nonlinear registration to the Montreal Neurological Institute standard space, and the computed transformation matrix was then applied to the corresponding DTI indices, MWF, *R1*, and *R2* maps. Fourteen white matter regions of interest (ROIs) were defined from the Montreal Neurological Institute structural atlas corresponding to the whole brain, the frontal, parietal, temporal, and occipital lobes, cerebellum, corpus callosum, internal capsule, cerebral peduncle, corona radiata, thalamic radiation, fronto-occipital fasciculus, longitudinal fasciculus, and forceps. ROIs were eroded to reduce partial volume effect. Within each ROI, the mean FA, RD, MD, AxD, MWF, *R1*, and *R2* values were calculated.

Systolic and Diastolic Blood Pressures

Systolic blood pressure and diastolic blood pressure were recorded 3 times in both arms in a seated position using a mercury sphygmomanometer sized to the arm of each participant, and the mean of the systolic and diastolic measurements were used in the subsequent analyses.[47] Hypertension was defined as a systolic blood pressure greater than or equal to 140 mm Hg, a diastolic blood pressure greater than or equal to 90 mm Hg, or the use of prescription hypertension medications.

Statistical Analysis

To investigate the effect of hypertension on relaxometry (MWF, *R1*, *R2*) and diffusion (FA, MD, RD, AxD) MRI metrics, a multiple

linear regression analysis was applied using MWF, *R1*, *R2*, FA, MD, RD, or AxD within each ROI as the dependent variable and hypertension status, smoking status, systolic blood pressure, diabetes, cholesterol, age, and sex as independent variables. In all cases, the threshold for statistical significance was $P<0.05$, while for close-to-significance was taken as $P<0.1$ after correction for multiple ROI comparisons using the false discovery rate method.[48,49] All calculations were performed with MATLAB software (MathWorks, Natick, MA).

RESULTS

Participants Demographic Characteristics

Demographic characteristics of the participants are shown in Table 1. After restricting the age range to participants of 40+ years and excluding 6 participants with either cognitive impairment, missing data or bad quality images due to severe motion artifacts, the final cohort consisted of 90 cognitively unimpaired volunteers (mean±SD MMSE=28.8±1.3) ranging in age from 40 to 94 years (64.6±17.1 years). Of this cohort, 49 (54.4%) were men, 30 (33.3%) were identified as cigarette smokers while 59 (65.6%) as nonsmokers. Among the cohort, 27 were hypertensive (30.0%), 23 of which taking antihypertensive medication. This cohort also included 3 participants (3.3%) with diabetes (2 of them were hypertensive), while 87 participants were nondiabetic (96.7%). The mean±SD values of the systolic blood pressure and diastolic blood pressure were 117.6±14.5 and 68.5±8.6, respectively, and the mean±SD values of cholesterol level were 183.0±35.1. Stratification of this cohort into hypertensive and control groups showed that, compared to the control group, the hypertensive group exhibits significantly ($P<0.05$) higher mean values of age and systolic blood pressure but a significantly ($P<0.05$) lower mean value of cholesterol level. The mean diastolic blood pressure was not significantly ($P>0.1$) different between the 2 groups.

Associations Between Hypertension and Cerebral Microstructure

Figure 1 shows the MWF, *R1* and *R2* relaxometry parameter maps of either hypertensive or nonhypertensive participants within an age range of 70 to 94 years. This limited age range minimizes the potential effect of age on derived MR parameter maps for this qualitative analysis (statistical quantification of the effect of age as a covariate will be presented below [Tables 2 and 3]). Visual inspection indicates that, overall, hypertensive participants exhibit lower regional MWF, *R1* and *R2* values as compared with nonhypertensive participants. These qualitative results suggest a potentially strong association between hypertension and myelin content.

Similarly, Figure 2 shows the FA, MD, RD, and AxD DTI parameter maps of either hypertensive or nonhypertensive participants within an age range of 70 to 94 years. Again, this limited age range is used to minimize the potential effect of age on derived DTI parameter

Table 1. Demographic Characteristics of Participants of the Study Cohort

	Full cohort	Hypertensive	Nonhypertensive
Sample size	N=90	n=27 (30.0%)	n=63 (70.0%)
Age, y; mean±SD (min–max)	64.6±17.1 (40–94)	76.0±14.1* (41–94)	59.7±15.9* (40–94)
Sex			
Male, N (%)	49 (54.4%)	15 (55.6%)	34 (54.0%)
Female, N (%)	41 (45.6%)	12 (44.4%)	29 (46.0%)
Smoker			
Smokers, N (%)	30 (33.3%)	12 (44.4%)	18 (28.6%)
Nonsmokers, N (%)	59 (65.6%)	15 (55.6%)	44 (69.8%)
Other, N (%)	1 (1.1%)	0 (0.0%)	1 (1.6%)
Diabetes			
Diabetic, N (%)	3 (3.3%)	2 (7.4%)	1 (1.6%)
Nondiabetic, N (%)	87 (96.7%)	25 (92.6%)	62 (98.4%)
SBP, mm Hg; mean±SD (min–max)	117.6±14.5 (89–161)	125.7±15.7* (106–161)	114.2±12.7* (89–139)
DBP, mm Hg; mean±SD (min–max)	68.5±8.6 (50–87)	66.4±9.8 (50–87)	69.3±8.0 (50–86)
Cholesterol, mean±SD (min–max)	183.0±35.1 (116–270)	169.7±37.8* (120–270)	188.7±32.5* (116–265)

DBP indicates diastolic blood pressure; max, maximum; min, minimum; and SBP, systolic blood pressure.
*Significant mean difference ($P<0.05$) between the hypertensive and the control groups.

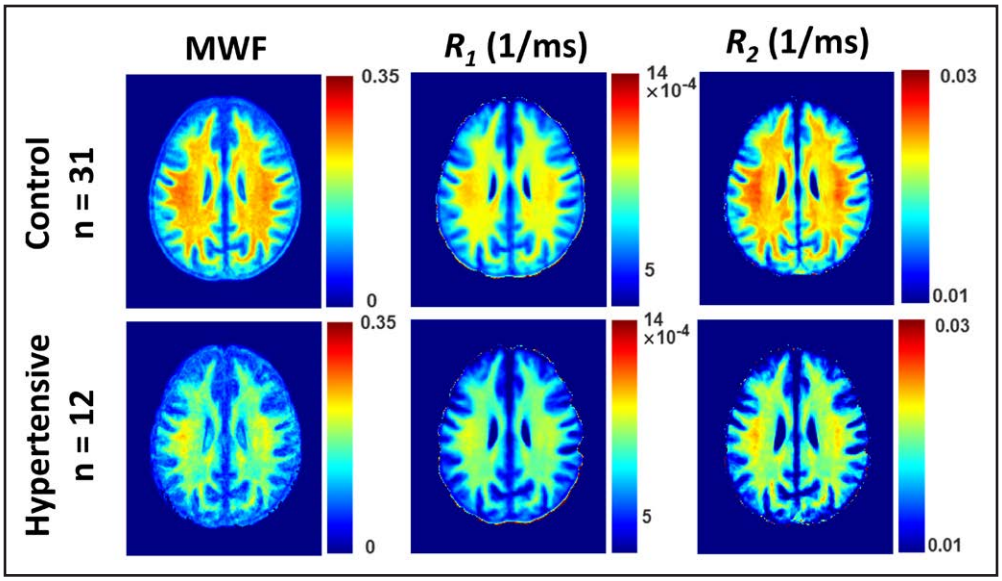

Figure 1. Examples of myelin water fraction (MWF), R_1 and R_2 parameter maps averaged across participants drawn from a limited age range (70–94 years) either hypertensive (n=12) or nonhypertensive (n=31) to mitigate the effect of age.
Results are shown for a representative slice. Visual inspection indicates that overall hypertensive patients exhibit lower regional MWF, R_1 and R_2 values, as compared with controls. R_1 indicates longitudinal relaxation rate; and R_2, transverse relaxation rate.

maps for this qualitative analysis. Visual inspection indicates that, overall, hypertensive participants exhibit lower FA and higher MD, RD, and AxD values. In other words, hypertension is associated with higher diffusivities and a lower level of water diffusion. These qualitative results provide further support that hypertension is associated with reduced microstructural white matter integrity.

Table 2 summarizes the results of the multiple regression analysis of MWF, *R1* and *R2* versus hypertension and age in 14 white matter ROIs. In agreement with Figure 1, there are significant ($P<0.05$), or close-to-significant ($P<0.1$), negative correlations after false discovery rate correction, between hypertension and MWF or *R2* in all regions but the cerebellum and cerebral peduncles, and between hypertension and *R1* in all regions but the cerebellum. This is clearly seen in Figure 3 indicating that the hypertensive patients exhibit lower parameter values as compared with the control group. It was also found that the corpus callosum and the corona radiata exhibited the steepest slopes in the correlations between hypertension and MWF, *R1* and *R2*. Furthermore, as expected, age was found to be a significant covariate with hypertension and exhibited negative slopes with respect to all metrics except for *R1* in the cerebral peduncles (Table 2; Figure 3). Finally, the regression results for all the independent parameters included in the regression model are shown in the Supplemental Material.

Table 3 summarizes the results of the multiple regression analysis of FA, MD, RD, and AxD versus hypertension and age in the 14 white matter ROIs studied after controlling for relevant covariates. There are significant ($P<0.05$), or close-to-significant ($P<0.1$), negative correlations after false discovery rate correction, between FA and hypertension and positive correlations with MD, RD, and AxD in most ROIs investigated. Examples of these association are illustrated shown in Figure 3. Here, we found that the steepest slopes in the correlation between hypertension and FA, MD, RD, and AxD were found in the temporal lobe, fronto-occipital fasciculus, and the internal capsules. We note that in contrast to the results of the multicomponent relaxometry analysis, less ROIs were found to be statistically significant between hypertensive and control groups, with the parietal lobe and forceps regions found to be insignificant in the correlation between hypertension and diffusivity metrics. However, the overall trend of the data follows the paradigm of impaired white matter microstructural integrity. Furthermore, in all ROIs investigated, the effect of age was found to be significant with respect to all metrics (Table 3; Figure 3). Finally, the regression results for all the independent parameters included in the regression model are shown in the Supplemental Material.

DISCUSSION

In this MRI study, using advanced multicomponent relaxometry and DTI analyses for both direct and indirect measurements of myelin content, we found that the hypertension status is associated with lower regional myelin content as measured by the MWF, *R1, R2*, and DTI metrics (FA, MD, RD, and AxD). These regional associations were observed in a cohort of well-characterized, cognitively unimpaired, adults. These results provide further evidence of the association between a well-known cardiovascular risk factor, specifically hypertension, and cerebral white matter tissue integrity in the absence of

Table 2. Regression Coefficient (β), Including SE, and Significance (*P* Value After FDR) of Relaxometry Metrics (MWF, R_1, and R_2) Versus Hypertension and Age Across 14 WM ROIs

ROIs	MWF		R_1		R_2	
	Hypertension	Age	Hypertension	Age	Hypertension	Age
	β (SE)×10^{-2}	β (SE)×10^{-4}	β (SE)×10^{-5}	β (SE) ×10^{-6}	β (SE)×10^{-3}	β (SE)×10^{-5}
WB	−1.97 (0.68)	−9.64 (1.76)	−5.76 (1.74)	−1.71 (0.45)	−1.20 (0.46)	−6.12 (1.17)
	0.010*	<0.001*	0.004*	<0.001*	0.021*	<0.001*
FL	−2.43 (0.67)	−11.2 (1.73)	−6.77 (1.61)	−2.06 (0.41)	−1.45 (0.45)	−6.95 (1.15)
	0.006*	<0.001*	0.001*	<0.001*	0.009*	<0.001*
OL	−1.55 (0.87)	−8.43 (2.23)	−4.18 (1.98)	−1.41 (0.51)	−1.19 (0.57)	−5.61 (1.47)
	0.090*	<0.001*	0.043*	0.008*	0.052*	<0.001*
PL	−2.41 (0.78)	−10.1 (2.00)	−6.05 (1.75)	−1.87 (0.45)	−1.35 (0.53)	−7.06 (1.37)
	0.010*	<0.001*	0.003*	<0.001*	0.021*	<0.001*
TL	−1.84 (0.82)	−9.28 (2.10)	−4.91 (1.83)	−1.77 (0.47)	−1.28 (0.54)	−5.55 (1.38)
	0.038*	<0.001*	0.011*	<0.001*	0.027*	<0.001*
CRB	−0.50 (0.73)	−6.70 (1.89)	−2.63 (1.78)	−1.09 (0.46)	−0.20 (0.51)	−4.71 (1.30)
	0.500*	<0.001*	0.145*	0.021*	0.693*	<0.001*
CC	−2.06 (0.69)	−9.01 (1.77)	−7.41 (1.82)	−1.90 (0.47)	−1.72 (0.55)	−6.78 (1.42)
	0.010*	<0.001*	0.001*	<0.001*	0.009*	<0.001*
IC	−1.40 (0.71)	−9.61 (1.83)	−4.91 (1.74)	−1.77 (0.45)	−0.84 (0.43)	−5.48 (1.11)
	0.067*	<0.001*	0.008*	<0.001*	0.065*	<0.001*
CR	−3.03 (0.88)	−11.8 (2.27)	−7.79 (1.93)	−2.16 (0.50)	−1.71 (0.53)	−5.84 (1.37)
	0.006*	<0.001*	0.001*	<0.001*	0.009*	<0.001*
CP	−0.70 (0.63)	−4.07 (1.61)	−3.70 (1.77)	−0.50 (0.46)	−0.31 (0.48)	−3.54 (1.23)
	0.285*	0.013*	0.043*	0.273*	0.561*	<0.001*
TR	−2.20 (0.83)	−10.1 (2.14)	−5.70 (1.88)	−2.04 (0.48)	−1.38 (0.53)	−5.34 (1.37)
	0.015*	<0.001*	0.006*	<0.001*	0.021*	0.005*
FOF	−2.37 (0.77)	−10.7 (1.98)	−5.95 (1.85)	−2.09 (0.48)	−1.52 (0.51)	−6.71 (1.30)
	0.010*	<0.001*	0.004*	<0.001*	0.010*	<0.001*
LF	−2.28 (0.80)	−9.92 (2.06)	−5.63 (1.88)	−2.02 (0.49)	−1.29 (0.50)	−5.35 (1.29)
	0.010*	<0.001*	0.006*	<0.001*	0.021*	<0.001*
Fr	−2.24 (0.76)	−10.6 (1.95)	−6.12 (1.87)	−2.02 (0.48)	−1.57 (0.51)	−6.38 (1.30)
	0.010*	<0.001*	0.004*	<0.001*	0.009*	<0.001*

The multiple regression model is given by: MRI ~β_0+β_{age}×age+$\beta_{Hypertension}$×Hypertension+$\beta_{Smoking}$×Smoking+β_{SBP}×SBP+β_{sex}×sex+$\beta_{Diabetes}$×Diabetes+$\beta_{Cholesterol}$×Cholesterol, where MRI corresponds to MWF, R_1 or R_2. The regression model accounted for sex, smoking status, diabetes status and hypertension as categorical variables. CC indicates corpus callosum; CR, corona radiata; CRB, cerebellum; FDR, false discovery rate; FL, frontal lobe; FOF, fronto-occipital fasciculus; Fr, forceps.; IC, internal capsule; LF, longitudinal fasciculus; MRI, magnetic resonance imaging; MWF, myelin water fraction; OL, occipital lobe; PL, parietal lobe; R1, Longitudinal rate of relaxation; R2, Transverse rate of relaxation; ROI, region-of-interest; SBP, systolic blood pressure; SE, standard error; TL, temporal lobe; TR, thalamic radiation; WB, whole brain; and WM, white matter.

*P value indicates statistical significance (P<0.05) or close-to-significance (P<0.1), after FDR correction. We note that the regression results for all the independent parameters included in the regression model are shown in the Tables S1 through S3.

cognitive impairment. Furthermore, to our knowledge, this is the first investigation to indicate a direct association between hypertension and myelin deterioration, as measured by a specific proxy of myelin content (ie, MWF). In our analysis, we found that hypertension was associated with higher MD, RD, and AxD values and lower MWF, FA, *R1*, and *R2* values. Our DTI results agree with previous DTI studies that have also shown a connection between cardiovascular risk factors, especially hypertension, and decreased cerebral microstructural integrity.[9–12,50–52]

While our relaxometry results, in conjunction with our DTI results, do not prove causality, they support the paradigm that hypertension impairs white matter microstructural integrity, especially the myelination process.[5,53] Indeed, studies have revealed association between increased arterial stiffness and hypertension during the aging process.[54–56] One of these paradigms suggests that vascular dysregulation due to potential synergetic effects of arterial remodeling and blood pressure may lead to transient reductions in cerebral blood flow, consequently resulting in transient decreased glucose transport into brain and hypoxia, and concomitant myelin injury.[35] Indeed, recent works have demonstrated that deficits in cerebral blood flow are directly linked to

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Table 3. Regression Coefficient (β), Including SE, and Significance (*P* value After FDR) of Diffusion Tensor Imaging metrics (FA, MD, RD, and AxD) Versus Hypertension and Age Across 14 WM ROIs

ROI	FA		MD		RD		AxD	
	Hypertension	Age	Hypertension	Age	Hypertension	Age	Hypertension	Age
	β (SE)×10^{-2}	β (SE) ×10^{-4}	β (SE)×10^{-5}	β (SE)×10^{-6}	β (SE)×10^{-5}	β (SE)×10^{-6}	β (SE)×10^{-5}	β (SE)×10^{-6}
WB	−1.20 (0.53)	−6.87 (1.36)	1.68 (1.47)	2.46 (0.38)	2.62 (1.60)	2.87 (0.41)	3.07 (1.70)	3.06 (0.43)
	0.041*	<0.001*	0.276	<0.001*	0.122	<0.001*	0.086*	<0.001*
FL	—2.51 (0.51)	−8.65 (1.31)	2.77 (1.67)	3.92 (0.43)	4.29 (1.76)	4.34 (0.45)	5.01 (1.83)	4.54 (0.47)
	<0.001*	<0.001*	0.128	<0.001*	0.026*	<0.001*	0.012*	<0.001*
OL	−1.81 (0.56)	−10.3 (1.44)	2.99 (0.91)	2.03 (0.23)	3.99 (1.13)	2.75 (0.29)	4.47 (1.29)	3.11 (0.33)
	0.006*	<0.001*	0.021*	<0.001*	0.002*	<0.001*	0.003*	<0.001*
PL	−1.08 (0.78)	−5.02 (2.00)	2.21 (1.52)	0.67 (0.39)	1.84 (1.46)	1.03 (0.37)	1.61 (1.59)	1.21 (0.41)
	0.168	0.015*	0.175	0.089*	0.229	0.004*	0.336	0.004*
TL	−5.52 (1.36)	−19.3 (3.49)	5.67 (2.12)	2.23 (0.54)	10.1 (2.60)	3.75 (0.67)	12.3 (3.16)	4.43 (0.81)
	<0.001*	<0.001*	0.032*	<0.001*	0.002*	<0.001*	0.002*	<0.001*
CRB	−2.50 (1.14)	−7.99 (2.93)	4.55 (2.01)	2.95 (0.52)	5.21 (2.17)	2.40 (0.56)	5.54 (2.36)	2.10 (0.60)
	0.044*	0.009*	0.042*	<0.001*	0.026*	<0.001*	0.030*	<0.001*
CC	−1.87 (0.70)	−11.8 (1.79)	5.79 (2.02)	1.98 (0.52)	6.10 (1.85)	2.42 (0.47)	6.27 (1.83)	2.62 (0.47)
	0.021*	<0.001*	0.030*	<0.001*	0.004*	<0.001*	0.003*	<0.001*
IC	−2.60 (1.14)	−6.35 (2.93)	4.05 (1.80),	2.34 (0.46)	6.02 (1.90)	2.33 (0.49)	7.07 (2.22)	2.27 (0.57)
	0.041*	0.033*	0.042*	<0.001*	0.005*	<0.001*	0.004*	<0.001*
CR	−2.04 (0.64)	−10.4 (1.64)	2.97 (1.21)	1.32 (0.31)	4.27 (1.21)	1.84 (0.31)	4.90 (1.30)	2.09 (0.33)
	0.006*	<0.001*	0.037*	<0.001*	0.002*	<0.001*	0.002*	<0.001*
CP	−1.64 (0.92)	−7.91 (2.35)	5.01 (1.78)	2.45 (0.46)	5.30 (1.78)	2.49 (0.46)	5.36 (1.91)	2.52 (0.49)
	0.091*	0.001*	0.030*	<0.001*	0.007*	<0.001*	0.011*	<0.001*
TR	−1.76 (0.77)	−6.86 (1.98)	2.82 (1.11)	1.11 (0.28)	3.76 (1.06)	1.41 (0.27)	4.22 (1.22)	1.56 (0.31)
	0.041*	0.001*	0.036*	<0.001*	0.002*	<0.001*	0.003*	<0.001*
FOF	−3.24 (0.90)	−15.0 (2.29)	3.52 (1.56)	1.36 (0.40)	6.11 (1.94)	2.60 (0.50)	7.40 (2.21)	3.21 (0.57)
	0.002*	<0.001*	0.042*	0.001*	0.005*	<0.001*	0.003*	<0.001*
LF	−6.49 (0.34)	−7.54 (0.87)	3.75 (2.14)	6.10 (0.55)	3.86 (2.13)	6.35 (0.55)	3.87 (2.14)	6.47 (0.55)
	0.074*	<0.001*	0.119	<0.001*	0.094*	<0.001*	0.086*	<0.001*
Fr	−6.92 (0.45)	−8.91 (1.15)	2.16 (2.98)	7.84 (0.76)	2.24 (3.02)	8.21 (0.77)	2.23 (3.05)	8.41 (0.78)
	0.136	<0.001*	0.470	<0.001*	0.460	<0.001*	0.465	<0.001*

The multiple regression model is given by: MRI ~ $\beta_0+\beta_{age}\times$age$+\beta_{Hypertension}\times$Hypertension$+\beta_{Smoking}\times$Smoking$+\beta_{SBP}\times$SBP$+\beta_{sex}\times$sex$+\beta_{Diabetes}\times$Diabetes$+\beta_{Cholesterol}\times$Cholesterol, where MRI corresponds to FA, MD, RD, and AxD. The regression model accounted for sex, smoking status, diabetes status, and hypertension as categorical variables. AxD indicates axial diffusivity; CC, corpus callosum; CR, corona radiata; CRB, cerebellum; FA, fractional anisotropy; FDR, false discovery rate; FL, frontal lobe; FOF, fronto-occipital fasciculus; Fr, forceps; IC, internal capsule; LF, longitudinal fasciculus; MD, medial diffusivity; OL, occipital lobe; PL, parietal lobe; RD, radial diffusivity; ROI, region-of-interest; SBP, systolic blood pressure; SE, standard error; TL, temporal lobe; TR, thalamic radiation; WB, whole brain; and WM, white matter.

*P value indicates statistical significance ($P<0.05$) or close-to-significance ($P<0.1$), after FDR correction. We note that the regression results for all the independent parameters included in the regression model are shown in the Tables S4 through S7.

reductions in cerebral tissue integrity. This association is present to a greater extent with white matter tissue damage.[26,41,57] In fact, myelin maintenance through oligodendrocyte metabolism is an energy-demanding process, and therefore myelin homeostasis is particularly sensitive to hypoperfusion and consequent hypoxia or lack of essential nutrients for myelin synthesis.[58,59] Recent in vitro studies have shown that oligodendrocytes are substantially more vulnerable to hypoxia and reduced supply of substrates that provide energy as can occur from hypoperfusion, when compared with other glial cells such as microglia and astroglia.[60] Furthermore, it has been shown that hypertension also interferes with perivascular glymphatic drainage and blood-brain permeability. This would result in reduced drainage of toxic metabolites that adversely impact oligodendrocytes, the main cells synthesizing and maintaining myelin in the brain.[61] Finally, interruption in the myelination process could result from chronic inflammation. Indeed, animal studies have demonstrated that chronically elevated blood pressure leads to adverse glial activation and increased brain inflammatory mediators that can be harmful to the myelin sheets and the normal functioning of oligodendrocyte cells.[62] Nevertheless, despite these potential plausible mechanisms, further studies, especially of a longitudinal nature, are still required to

shed light on the association between blood pressure and myelination.

We found the steepest slopes in the correlations between hypertension and MWF, *R1* and *R2*, in the corpus callosum, fronto-occipital fasciculus and corona radiata cerebral regions (Table 2). Numerous studies have found that these brain regions are particularly susceptible to microstructural damages due to elevated blood pressure.[63–65] Interestingly, these brain structures have also been shown to exhibit higher sensitivity to the cerebral blood supply.[12,20,66,67] For example, the corpus callosum has an especially high level of metabolic demand, receiving blood from the anterior communicating, anterior pericallosal, and posterior cerebral arteries.[68] Although ischemia in this region is rare due to the trifurcated nature of the vascular pathway, the energy-demanding process of myelination could be impeded from even minor changes in blood flow, such as those that occur from hypertension.[69,70] However, it should be emphasized that the corpus callosum and the fronto-occipital fasciculus and corona radiata cerebral regions exhibit uniform myelination throughout their structures which may have led to better detection of the association between hypertension and myelination.

Longitudinal studies have found that antihypertensive medication has a protective effect on the brain and helps to reduce the rate of cognitive decline and neurodegeneration, including in Alzheimer's disease.[71,72] These studies consistently find that elevated blood pressure in midlife is more closely associated with cognitive decline when compared with elevated blood pressure in late life.[73,74] This could possibly be due to the slow progression of hypertensive arterial remodeling eventually leading to reduced blood flow post-ischemia.[5] Interestingly, among the 27 hypertensive subjects in our study, 23 subjects were taking antihypertensive medication at the time of the scan. Although it is unclear whether the antihypertensive medication had some level of a protective effect on these participants, it is interesting to note that participants undergoing treatment still had significantly lower myelin content or higher microstructural damage in many of the regions analyzed (Table 1). We conjecture that this may be due to either microstructural damage being done before the treatment of the antihypertensive medication or as a demonstration of the possible limitations of the antihypertensive medication on protecting the overall cerebral microstructure long term (Figures 1 and 2). Unfortunately, the information regarding the duration under medication was not available to further explore these interesting aspects including the effect of medication duration on myelination.

Although our investigation examined a relatively large cohort and used advanced MRI methodology to probe myelin content and obtain diffusion metrics, our work has certain limitations. The cross-sectional nature of the study precludes us from drawing any causal link between hypertension and demyelination; future longitudinal studies are needed to further support this potential association. We also note that the causal

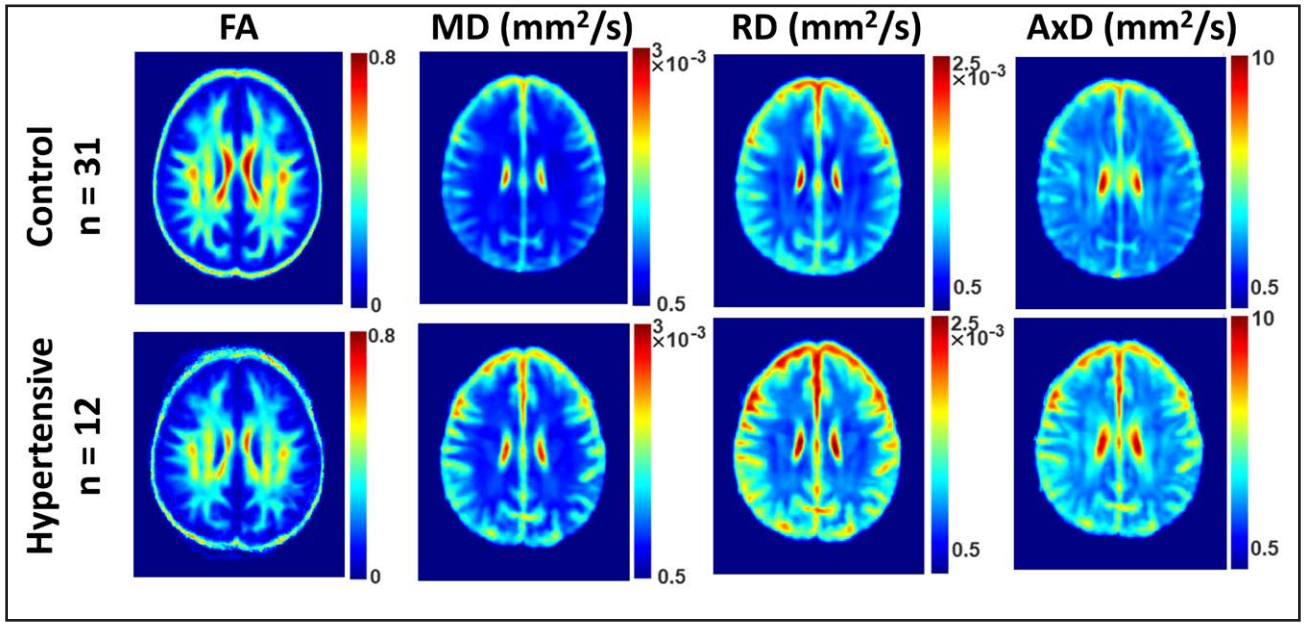

Figure 2. Examples of fractional anisotropy (FA), medial diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AxD) parameter maps averaged across participants drawn from a limited age range (70–94 years) either hypertensive (n=12) or nonhypertensive (n=31) to mitigate the effect of age.
Results are shown for a representative slice. Visual inspection indicates that, overall, hypertensive participants exhibit lower FA and higher MD, RD, and AxD.

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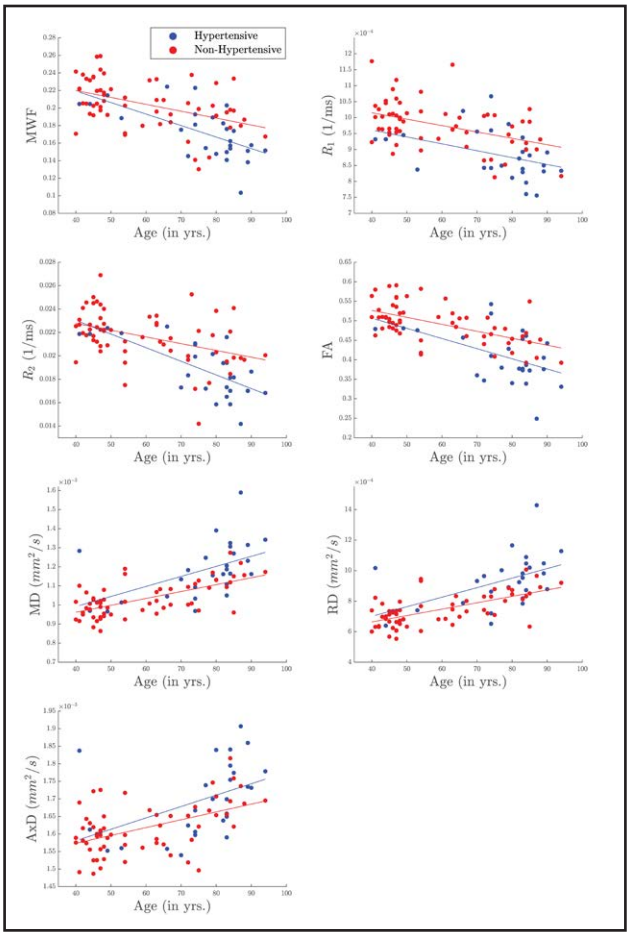

Figure 3. Examples of scatter plots of myelin water fraction (MWF), R_1, R_2, fractional anisotropy (FA), medial diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AxD) as a function of age stratified by groups.
The hypertensive group is indicated by the blue color while the control group is indicated by the red color. Results were obtained from the corpus callosum ROI for MWF, R_1 and R_2, while from the temporal lobes ROIs for FA, MD, RD, and AxD. It is readily seen that derived MWF, R_1, R_2, and FA parameter values decrease with age while the diffusivity values increase with age, as expected. Importantly, the hypertensive patients exhibit lower MWF, R_1, R_2, and FA parameter values or higher diffusivity values as compared to control. R_1 indicates longitudinal relaxation rate; and R_2, transverse relaxation rate.

relationship between hypertension and myelination is difficult to determine as hypertension commonly occurs concomitant with many other cardiovascular risk factors, and we cannot control for all of them in our limited multiple linear regression model given the cohort size. Finally, determination of MR parameters can be biased due to several biological and methodological factors. These include, but are not limited to, the effects of magnetization transfer between macromolecules and free water protons, exchange between water pools, J-coupling, off-resonance, spin locking effects, water diffusion within different compartments, flow, temperature, hydration, internal gradients, and architectural features, including fiber fanning or crossing.[57] Moreover, while the local distortions and motion artefacts in the DW images were corrected, we used the original b-vectors used in the acquisition. This could have introduced some bias in derived DTI indices. Finally, we did not control for white matter hyperintensity. Our inspection of this dataset revealed that white matter hyperintensities were limited to only a few subjects. This was expected given the very healthy nature of the BLSA and GESTALT cohorts. Further, the white matter hyperintensities were limited to small areas in the brain so that their impact in derived parameter values is negligible given the very large ROIs used in this study.

Perspectives

This study provides new insights into the association between hypertension and axonal demyelination among cognitively normal individuals spanning a wide age range. This work motivates further investigations to elucidate the extent to which hypertension and myelination are related in the pathological progression of neurodegenerative diseases, including in Alzheimer's disease and dementias. This study will provide guidance towards new targets for intervention through re-enforcing myelination and controlling blood pressure.

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Affiliation

Laboratory of Clinical Investigation (J.P.L., M.E.F., Z.G., M.A.B.S.A., J.M.E., M.B.) and Translational Gerontology Branch (L.F.), National Institute on Aging, National Institutes of Health, Baltimore, MD.

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Disclosures

None.

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