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Blood pressure and neuropsychiatric symptoms in old age

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Chapter 7

Lower blood pressure and grey matter integrity loss in older persons

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Abstract

Background

In contrast to middle age, it is unclear whether blood pressure (BP) in older persons is associated with cerebral small vessel disease (cSVD). The authors evaluated the association of BP with signs of cSVD as well as grey and white matter integrity in older persons.

Methods

In 220 participants aged 75 years and older from the Discontinuation of Antihypertensive Treatment in the Elderly (DANTE) study, cSVD was assessed with conventional magnetic resonance imaging, and microstructural integrity with diffusion tensor and magnetization transfer (MT) imaging.

Results

BP measures were not associated with cSVD. However, lower systolic and diastolic BP and mean arterial pressure were associated with decreased grey matter MT ratio peak height and MT ratio in cortical grey matter. Mean arterial pressure was also associated with increased grey matter diffusivity.

Conclusion

A lower level of BP was especially associated with worse grey matter integrity. Results suggest that not only upper but preferably lower thresholds of BP values should be observed in older persons.

Introduction

High blood pressure (BP) is related to increased risk of cerebral small vessel disease in middle age, typically including white matter hyperintensities (WMHs),[1-10] lacunar infarcts,[11-13] and microbleeds[14-17] on magnetic resonance imaging (MRI). Apart from these on MRI visual focal changes, more widespread subtle changes in the microstructural integrity of the cerebral white matter have been reported.[18-21]

In older persons, the association of BP with MRI findings may be may be different than in middle-aged persons, since low BP, rather than high BP has been associated with cerebral damage [1;2;22] and worse outcomes such as risk of ischemic stroke,[23;24] and mortality.[25] In these studies it has been suggested that this effect may be caused by hypoperfusion, especially in older people with arteriosclerotic damage or a history of cardiovascular disease. Thus, these persons may be better off with higher BP levels, whereby perfusion is maintained and brain integrity preserved.[26;27] To our knowledge no studies have assessed the relationship between BP and manifestation of small vessel disease, in combination with measurements of grey and white microstructural brain integrity in older persons.

The aim of the present cross-sectional study was to explore the associations of BP with manifestations of small vessel disease and microstructural brain integrity in both grey and white matter in older persons.

Methods

Participants

Participants for this MRI sub-study were included from the Discontinuation of Antihypertensive Treatment in the Elderly (DANTE) trial, a community-based randomized non-blinded clinical trial assessing the effect of temporary discontinuation of antihypertensive therapy on neuropsychological functioning in older persons with mild cognitive dysfunction. Inclusion criteria were age 75 years and older, use of antihypertensive medication, presence of mild cognitive dysfunction (according to Mini-Mental State Examination score 21–27), and current systolic blood pressure (SBP) ≤ 160 mm Hg (or ≤ 140 mm Hg for persons with diabetes, or myocardial infarction, peripheral artery vascular disease, or coronary reperfusion procedures more than 3 years ago). Current BP was determined based on the last BP measurement obtained from the general practitioners' electronic medical record. Exclusion criteria were a history of stroke or transient ischemic attack, a recent (≤ 3 years) myocardial infarction or recent coronary reperfusion procedure, current angina pectoris, cardiac arrhythmias, heart failure, use of antihypertensive medication other than for hypertension, a clinical diagnosis of dementia, or a limited life expectancy.

The current study used baseline data of the MRI sub-study. From the 430 DANTE participants, 220 non-selected persons underwent MRI of the brain. The Medical Ethical committee of the Leiden University Medical Center approved the study, and written informed consent was obtained from all participants.

Blood pressure

SBP and diastolic blood pressure (DBP) were measured twice at baseline in a seated position in all participants using a fully automatic electronic sphygmomanometer (Omron M6 Comfort; Omron Healthcare, Inc, Lake Forest, IL). For analyses, the mean of the two measurements was calculated. Mean arterial pressure (MAP) was calculated as 1/3(SBP)+2/3(DBP), and pulse pressure (PP) as SBP–DBP.

MRI Acquisition

All MRI scans were acquired on a whole-body magnetic resonance system operating at a field strength of 3-T with a 32-channel head coil (Philips Medical Systems, Best, The Netherlands). Three-dimensional (3D) T1-weighted images were acquired with repetition time (TR)/echo time (TE)=9.7/4.6 ms, flip angle (FA)=8°, and a nominal voxel size of 1.1791.1791.4 mm. Fluid-Attenuated Inversion Recovery (FLAIR) images (TR/TE=11,000/125 ms, FA=90°), T2-weighted images (TR/TE=4200/80 ms, FA=90°), and T2*-weighted images (TR/TE=45/31 ms, FA=13°) were acquired. Diffusion tensor images (DTI) (TR/TE=9592/56 ms, FA=90°, 64 slices, 32 measurement directions, *b* value=1000) and magnetization transfer images (MTI) with and without a saturation pulse (TR/TE=100/11 ms, FA=9°) were acquired. DTI images and MTI images were available for 195 and 216 participants, respectively.

White Matter Hyperintensities, Lacunar Infarcts, and Microbleeds

MRI scans were visualized using Philips DICOM viewer R3.0-SP03 software (Philips Medical Systems). Cerebral ischemic damage was evaluated as previously reported.[28] In short, periventricular and subcortical WMHs were scored semi quantitatively. Periventricular WMHs were present when lateral, posterior, and anterior periventricular regions were scored ≥2. A lacunar infarct, assessed on FLAIR and T2- and 3D T1-weighted images, was defined as a parenchymal defect (signal intensity identical to cerebrospinal fluid on all sequences) of at least 3 mm in diameter, surrounded by a zone of parenchyma with increased signal intensity on T2-weighted and FLAIR images. Microbleeds were defined as focal areas of signal void (on T2 images), which increased in size on T2*-weighted images (blooming effect). Symmetric hypointensities in the basal ganglia, likely to represent calcifications or non-hemorrhagic iron deposits, were disregarded. All measurements were obtained blinded to participants' demographic and clinical information.

Image processing and analysis

MRI scans were analyzed with FMRIB software version 5.0.1. Library.[29] For the automated measurement of WMH volume, 3DT1-weighted and FLAIR images were skull stripped[30] and co-registered using the FMRIB's Linear Image Registration Tool (FLIRT).[31;32] The FLAIR image was affine-registered to MNI152 standard space using FLIRT. WMHs were extracted from FLAIR images with a conservative MNI152 white matter mask and a threshold was set to identify which white matter voxels were hyperintense, followed by manually checking and editing for quality control.

Using the FDT (FMRIB's Diffusion Toolbox), individual fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AxD) and radial diffusivity (RD) images were created.[33;34] Using FLIRT to a non-diffusion-weighted reference volume, original images were corrected for effects of head movement and eddy currents in the gradient coils. A diffusion tensor model was fitted to the corrected images to create individual FA, MD, AxD and RD images. For global quantification of brain tissue FA, MD, AxD, and RD, 3D T1 images were skull stripped,[35] segmented, [36] and aligned to MNI152 using FLIRT. Lower FA and higher MD, AxD and RD indicate poorer integrity.

For MTI data processing non-saturated (M0) and saturated (M1) images were co-registered to the 3D T1 image.[36] Individual magnetic transfer ratio (MTR) maps were calculated voxel by voxel. 3D T1 cortical grey and white matter masks were corrected for possible partial volume effects.[37] Per volume-of-interest MTR peak height, normalized for the size of the volume-of-interest, were calculated.[38] MTR peak height value of one participant exceeded three standard deviations and was excluded. Lower MTR peak height indicates poorer integrity.

For the voxel-based analysis, MTR grey matter maps were aligned to MNI152 using nonlinear transformation,[39] and averaged to create a reference template for MTR images. Individual grey matter MTR maps were nonlinearly registered to this template.[40] Voxel wise statistics were carried out with FSL randomise using permutation-based nonparametric testing (5000 permutations). Threshold-Free Cluster Enhancement was applied with a significance level set at $P<0.05$ Family Wise Error corrected for multiple comparisons. Age and sex of participants were inserted as covariates in the model.

Demographic and clinical variables

Demographic and clinical characteristics were obtained using a standardized interview. Education was dichotomized at 6 years of schooling (primary education only) and alcohol use at 14 units per week. Using structured questionnaires, information about medication and medical histories was obtained from the general practitioners.

Statistical analyses

Characteristics of the study participants are reported as mean (standard deviation), median (interquartile range) for continuous variables when appropriate, and number (percentage) for categorical variables.

For analyses, the SBP and DBP were both grouped into three clinically relevant categories: SBP<140 mm Hg, 140–159 mm Hg and ≥ 160 mm Hg, and DBP<80 mm Hg, 80–89 mm Hg, and ≥ 90 mm Hg. Since no clinically relevant cutoff values are known for MAP and PP, these were grouped into tertiles. Accordingly, the associations of clinically relevant groups of SBP, DBP, and tertiles of MAP and PP with parameters of small vessel disease and microstructural integrity were analyzed using logistic or linear regression analysis adjusting for age, sex, and duration of antihypertensive treatment. WMH volume was logarithmically transformed to ensure a normal distribution. Standardized *z* scores were calculated for the microstructural parameters using the following equation: (=test score−mean)/SD) (Figure 1). As SBP<140 mm Hg, 140–159 mm Hg, and ≥ 160 mm Hg groups included different percentages of persons with diabetes (27.3%, 18.7% and 13.0%, respectively), we performed additional analyses with further adjustment for diabetes.

To assess whether associations found were nonlinear, additional analyses were performed for which the lowest SBP group was grouped into three clinically relevant low BP categories: SBP 120 mm Hg, 120–129 mm Hg, and 130–140 mm Hg. In addition, we evaluated whether J-shaped relationships were present by adding quadratic terms of continuous BP measures to the model.

A *P* value of <0.05 was considered statistically significant. Data were analyzed using an exploratory approach therefore no formal adjustments for multiple comparisons were used. Statistical analysis was performed with SPSS software (version 20.0; SPSS, Chicago, IL).

Results

Table 1 summarizes the characteristics of the study participants. Mean age was 80.7 (SD 4.1) years; median Mini-Mental State Examination score was 26 (IQR 25–27), reflecting mild cognitive dysfunction; median WMH volume was 22 (IQR 9–56) mL; and lacunar infarcts or microbleeds were present in 59 (27%) and 55 (25%) of participants, respectively.

TABLE 1. Characteristics of participants

Characteristic	(n=220)
Demographic	
Age in years	80.7 (4.1)
Female	125 (56.8)
Lower education (≤ 6 years)	64 (29.1)
Clinical	
Current smoking	17 (7.7)
Alcohol ≥ 14 units/week	24 (10.9)
History of CVD[a]	20 (9.1)
Presence of chronic diseases[b]	135 (61.4)
MMSE (points)	26 (25-27)
Duration of antihypertensive treatment	
< 1 year	5 (2.3)
1-5 years	57 (25.9)
> 5 years	149 (67.7)
Blood pressure (mm Hg)	
Systolic	146 (21)
Diastolic	81 (11)
Mean arterial pressure	102 (13)
Pulse pressure	65 (15)
MRI	
WMH volume (ml)	22 (9-56)
Periventricular WMH	132 (60.0)
Subcortical WMH	113 (51.4)
Lacunar infarcts	59 (26.8)
Microbleeds	55 (25.0)

Data are presented as mean (standard deviation), median (interquartile range), or number (percentage) when appropriate. Abbreviations: MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; WMH, white matter hyperintensity.

[a] Cardiovascular disease (CVD) includes myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft.

[b] Chronic diseases include diabetes mellitus, Parkinson's disease, chronic obstructive pulmonary disease, malignancy, and osteoarthritis

No significant associations were found between SBP or DBP with volumes of WMH, presence of periventricular or subcortical WMH, lacunar infarcts, or microbleeds. There was also no significant association of MAP or PP with any of these parameters (Table 2).

TABLE 2. Parameters of small vessel disease in groups of systolic and diastolic blood pressure and tertiles of mean arterial pressure and pulse pressure

	Systolic blood pressure (mm Hg)					Diastolic blood pressure (mm Hg)				
Parameters of small vessel disease	**< 140 (n=88)**	**140-159 (n=75)**	**≥ 160 (n=57)**	***B*/OR (95% CI)**	***P* trend**	**< 80 (n=99)**	**80-89 (n=78)**	**≥ 90 (n=43)**	***B*/OR (95% CI)**	***P* trend**
Volume WMH, ml	34.8 (4.1)	38.7 (5.1)	38.1 (37.9)	0.02 (-0.19, 0.24)	0.84	33.2 (3.3)	40.4 (5.1)	46.2 (7.1)	0.09 (-0.14, 0.31)	0.45
Periventricular WMH, n (%)	54 (61.4)	45 (60.0)	33 (57.9)	0.93 (0.65, 1.32)	0.68	54 (54.5)	51 (61.4)	27 (62.8)	1.34 (0.92, 1.95)	0.13
Subcortical WMH, n (%)	46 (52.3)	38 (50.7)	29 (50.9)	1.04 (0.73, 1.48)	0.83	52 (52.2)	39 (50.0)	22 (51.2)	0.98 (0.68, 1.41)	0.90
Lacunar infarcts, n (%)	21 (24.1)	21 (28.0)	17 (29.8)	1.18 (0.79, 1.76)	0.41	27 (27.6)	20 (26.6)	12 (27.9)	1.04 (0.69, 1.57)	0.86
Microbleeds, n (%)	19 (22.1)	18 (25.0)	18 (32.1)	1.38(0.92, 2.08)	0.12	20 (20.6)	24 (32.0)	11 (26.2)	1.45 (0.95, 2.21)	0.09
Basal, n (%)	11 (12.8)	12 (16.7)	10 (17.9)	1.34 (0.82, 2.19)	0.25	12 (12.4)	13 (17.3)	8 (19.0)	1.61 (0.96, 2.70)	0.07
Lobar, n (%)	14 (16.3)	13 (18.1)	14 (25.0)	1.33 (0.84, 2.10)	0.23	15 (15.5)	18 (24.0)	8 (19.0)	1.40 (0.87, 2.27)	0.17
	Mean arterial pressure (mm Hg)					**Pulse pressure (mm Hg)**				
	< 97 (n=73)	**97-107 (n=73)**	**> 107 (n=74)**	***B*/OR (95% CI)**	***P* trend**	**< 58 (n=74)**	**58-69 (n=72)**	**> 69 (n=74)**	***B*/OR (95% CI)**	***P* trend**
Volume WMH (cc)	32.8 (3.8)	41.0 (5.1)	38.1 (5.1)	0.02 (-0.19, 0.23)	0.85	33.5 (4.4)	37.1 (4.9)	40.3 (4.9)	0.06 (-0.15, 0.26)	0.59
Periventricular WMH, n (%)	43 (58.9)	47 (64.4)	42 (56.8)	0.95 (0.46, 1.43)	0.78	46 (62.2)	46 (63.9)	40 (54.1)	0.81 (0.58, 1.15)	0.81
Subcortical WMH, n (%)	37 (50.7)	42 (57.5)	34 (45.9)	1.43 (0.67, 1.33)	0.74	38 (51.4)	36 (50.0)	39 (52.3)	1.11 (0.79, 1.56)	0.53
Lacunar infarcts, n (%)	18 (25.0)	22 (30.1)	19 (25.7)	1.04 (0.71, 1.52)	0.86	18 (24.7)	19 (26.4)	22 (29.7)	1.16 (0.79, 1.71)	0.46
Microbleeds, n (%)	15 (21.1)	18 (25.7)	22 (30.1)	1.40 (0.94, 2.10)	0.10	17 (23.9)	19 (27.1)	19 (26.0)	1.03 (0.69, 1.53)	0.89
Basal, n (%)	9 (12.7)	15 (12.9)	9 (20.5)	1.59 (0.97, 2.62)	0.07	10 (14.1)	11 (15.7)	12 (16.4)	1.06 (0.68, 1.76)	0.71
Lobar, n (%)	11 (15.5)	13 (18.6)	17 (23.3)	1.39 (0.88, 2.20)	0.16	12 (16.9)	14 (20.0)	15 (20.5)	1.05 (0.68, 1.63)	0.83

Data are presented as mean (standard error) or number (%), and Beta's or OR's (per increase in blood pressure group or tertile) and (95% confidence interval [CI]), adjusted for age, sex, and duration of antihypertensive treatment. Abbreviation: WMH, white matter hyperintensity. Missing values: n=3 for volume WMH, n=1 for lacunar infarcts, and n=6 for microbleeds.

TABLE 3. Grey and white matter microstructural parameters in groups of systolic and diastolic blood pressure and tertiles of mean arterial and pulse pressure

	Systolic blood pressure (mm Hg)					Diastolic blood pressure (mm Hg)				
Microstructural parameters	**< 140 (n=88)**	**140-159 (n=75)**	**≥ 160 (n=57)**	***B* (95% CI)**	***P* trend**	**< 80 (n=99)**	**80-89 (n=78)**	**≥ 90 (n=43)**	***B* (95% CI)**	***P* trend**
Grey matter										
peak height	65 (1.1)	66 (1.2)	70 (1.6)	2.4 (0.6, 4.2)	0.01	65 (1.1)	67 (1.2)	70 (1.70	2.3 (0.4, 4.1)	0.02
FA	166 (0.9)	170 (1.0)	168 (1.2)	1.4 (-0.2, 2.9)	0.08	168 (0.8)	169(1.1)	168 (1.3)	0.0 (-1.6, 1.6)	0.97
MD	1151 (7.7)	1149 (7.5)	1146 (10.9)	-5.1 (-15.8, 5.9)	0.35	1156 (7.3)	1155 (7.6)	1122 (11.8)	-9.2 (-20.2, 1.7)	0.10
AxD	1339 (8.3)	1341 (8.1)	1335 (11.8)	-4.2 (-15.7, 7.4)	0.48	1346 (7.9)	1345 (8.0)	1310 (12.9)	-9.4 (-21.2, 2.4)	0.12
RD	1057 (7.5)	1054 (7.3)	1051 (10.5)	-5.6 (-16.0, 4.7)	0.28	1061 (7.1)	1059 (7.4)	1028 (11.3)	-9.1 (-19.7, 1.4)	0.09
White matter										
peak height	103 (1.9)	107 (2.0)	109 (2.7)	2.8 (-0.4, 5.9)	0.08	104 (1.7)	107 (2.1)	110 (3.0)	2.3 (-0.9, 5.5)	0.16
FA	243 (2.0)	248 (2.3)	242 (2.6)	0.4(-2.9, 3.7)	0.83	244 (1.9)	245 (2.4)	244 (2.9)	-1.5 (-4.8, 1.9)	0.40
MD	1009 (6.5)	1006 (6.7)	1011 (9.0)	-1.3(-10.7, 8.1)	0.78	1011 (6.4)	1013 (6.9)	994 (9.2)	-1.6 (-11.3, 8.1)	0.75
AxD	1243 (6.2)	1245 (6.2)	1245 (8.5)	-0.5 (-9.2, 8.3)	0.91	1246 (6.0)	1250 (6.2)	1228 (8.9)	-2.1 (-11.1, 6.8)	0.64
RD	893 (6.8)	887 (7.1)	894 (9.4)	-1.7 (-11.7, 8.2)	0.73	894 (6.6)	895 (7.3)	877 (9.5)	-1.3 (-11.5, 9.0)	0.81
	Mean arterial pressure (mm Hg)					**Pulse pressure (mm Hg)**				
	< 97 (n=73)	**97-107 (n=73)**	**> 107 (n=74)**	***B* (95% CI)**	***P* trend**	**< 58 (n=74)**	**58-69 (n=72)**	**> 69 (n=74)**	***B* (95% CI)**	***P* trend**
Grey matter										
peak height	64 (1.2)	67 (1.3)	69 (1.3)	2.5 (0.8, 4.2)	0.01	65 (1.3)	67 (1.2)	67 (1.4)	1.6 (-0.2, 3.3)	0.08
FA	167 (1.0)	169 (1.0)	168 (1.1)	1.0 (-0.5, 2.5)	0.18	167 (1.0)	169 (1.1)	169 (1.0)	1.4 (-0.0, 2.9)	0.06
MD	1159 (8.4)	1150 (8.4)	1139 (8.5)	-10.7 (-20.9,-0.6)	0.04	1149 (7.9)	1148 (8.7)	1149 (8.7)	-7.8 (-17.9, 2.4)	0.13
AxD	1348 (9.0)	1342 (9.1)	1327 (9.2)	-10.7 (-21.7, 0.3)	0.06	1338 (8.5)	1339 (9.5)	1339 (9.3)	-7.2 (-18.2, 3.7)	0.20
RD	1065 (7.8)	1055 (8.1)	1044 (8.3)	-10.8 (-20.6, -1.0)	0.03	1155 (7.7)	1153 (8.4)	1154 (8.5)	-8.1 (-17.9, 1.7)	0.10
White matter										
peak height	102 (1.9)	106 (2.3)	109 (2.2)	3.3 (0.3, 6.3)	0.03	103 (2.3)	107 (1.9)	107 (2.2)	2.3 (-0.7, 5.3)	0.13
FA	243 (2.3)	245 (2.1)	245 (2.4)	0.9 (-2.3, 4.0)	0.59	242 (2.2)	246 (2.4)	245 (2.2)	2.1 (-1.1, 5.2)	0.19
MD	1014 (7.4)	1011 (6.8)	1002 (7.4)	-6.0 (-15.0, 3.0)	0.19	1011 (7.1)	1006 (7.2)	1008 (7.3)	-7.3 (-16.2, 1.6)	0.11
AxD	1247 (6.9)	1248 (6.5)	1237 (6.9)	-5.1 (-13.4, 3.3)	0.24	1246 (6.7)	1242 (6.7)	1244 (6.9)	-6.4 (-14.6, 1.9)	0.13
RD	897 (7.8)	893 (7.1)	884 (7.8)	-6.4 (-15.9, 3.1)	0.19	894 (7.4)	888 (7.6)	890 (7.6)	-7.8 (-17.2, 1.6)	0.10

Data are presented mean (standard error), Beta's (per increase in blood pressure group or tertile) and (95% confidence interval [CI]), adjusted for age, sex and duration of antihypertensive treatment. Bold values indicate statistical significance. Abbreviations: AxD, axial diffusivity $mm^2/s \times 10^6$; FA, fractional anisotropy value $\times 10^3$; MD, mean diffusivity $mm^2/s \times 10^6$; Peak height, normalized magnetization transfer ratio peak height value $\times 10^3$; RD, radial diffusivity $mm^2/s \times 10^6$. Missing values: n=5 for MTR peak height, n=15 for FA, MD, AxD and RD.

The associations of BP measures with microstructural parameters (MTI and DTI) are shown in Table 3. Our data show that both lower SBP and DBP were significantly associated ($P<0.05$) with decreased grey MTR peak height. Accordingly, lower MAP was also significantly associated with decreased grey matter MTR peak height ($P=0.01$). Moreover, lower MAP was significantly associated with decreased white matter MTR peak height and with increased MD and RD in the grey matter (all $P<0.05$). There were no significant associations between PP and any of the parameters of microstructural integrity.

The additional adjustments for diabetes, to explore whether associations could be affected by higher percentage of persons with diabetes in the subgroup having lower SBP, did not alter associations. SBP and DBP were still significantly associated with grey matter MTR peak height ($B=2.4$, [95% CI 0.6 to 4.2] $P=0.01$ and $B=2.3$ [95% CI 0.4 to 4.2] $P=0.02$, respectively). Whereas, MAP was still significantly associated with grey matter MTR peak height, MD, and RD in the grey matter ($B=2.5$ [95% CI 0.7 to 4.3] $P=0.01$, $B=-10.7$ [95% CI –21.0 to –0.4] $P=0.04$, and $B=-10.8$ [95% CI –20.8 to –0.9] $P=0.03$, respectively) and with white matter MTR peak height ($B=3.4$ [95% CI 0.4 to 6.5] $P=0.03$).

Modelling SBP in low BP groups and the analyses performed with quadratic terms of BP measures confirmed a linear relation. The effect size of the low clinical SBP categories and grey matter MTR peak height was $B=2.2$ (95% CI, –0.6 to 5.0), which was comparable to the associations found in the entire group; however, because of the small numbers in the low SBP groups (< 120 mm Hg: n=23; 120–129 mm Hg: n=24; and 130–140 mm Hg: n=42), this association was not statistically significant. Quadratic terms of continuous SBP, DBP, MAP, and PP were all not statistically significant.

Figure 1 shows forest plots of all BP measures and MTR peak height, FA, MD, AxD, and RD in grey matter. The direction of all of the associations is similar and indicates that lower SBP, DBP, and MAP are significantly associated with lower grey matter MTR peak height and lower MAP with higher MD and RD in the grey matter.

To investigate potential preferential focal associations between BP measures and MTR in cortical grey matter, VBM analysis was performed. Results of these voxel-based analyses are shown in Figure 2, indicating that mainly lower SBP, DBP, and MAP were statistically significant associated with a decrease of MTR in cortical grey matter with a symmetrical diffuse pattern in both hemispheres, with a slight preference for the frontal lobe. For PP, no cortical areas that demonstrated a significant association with MTR was found.

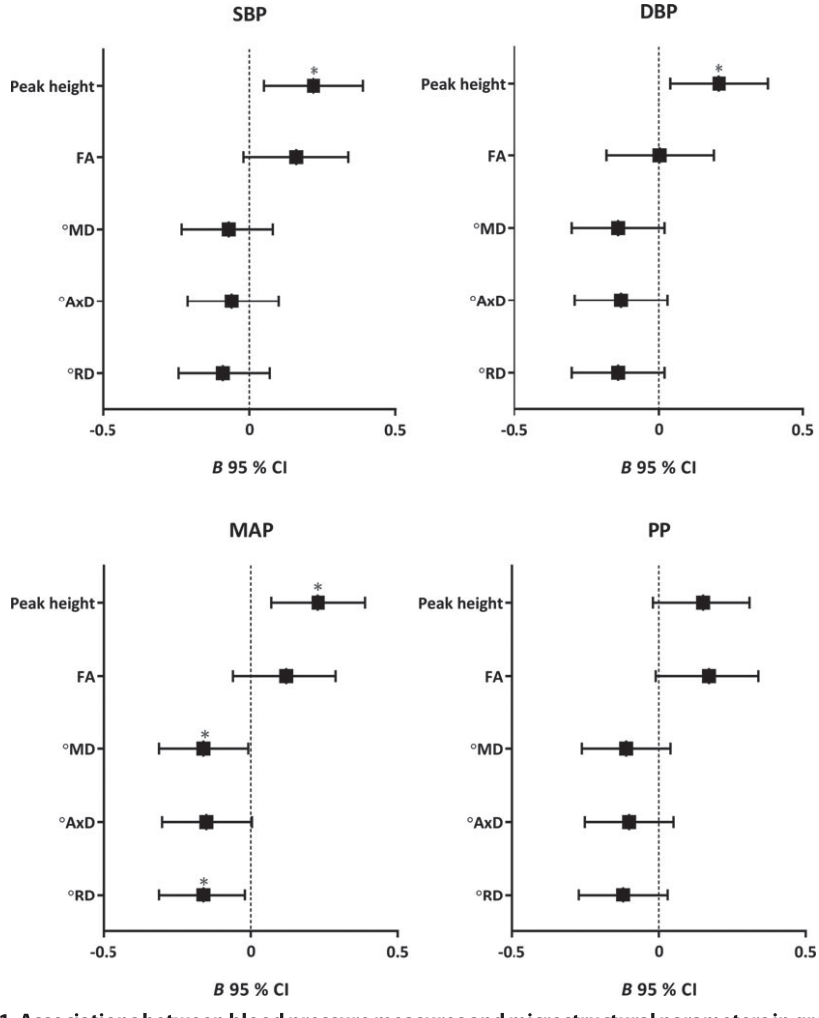

FIGURE 1. Associations between blood pressure measures and microstructural parameters in grey matter
B (95% confidence interval [CI]) of the associations of systolic (SBP), diastolic blood pressure (DBP) groups, mean arterial pressure (MAP) or pulse pressure (PP) tertiles, with *z* scores of magnetization transfer ratio peak height (peak height), fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AxD), and radial diffusivity (RD) in grey matter adjusted for age, sex, and duration of antihypertensive treatment.
*$P<0.05$. °Higher diffusivity indicates poorer microstructural integrity.

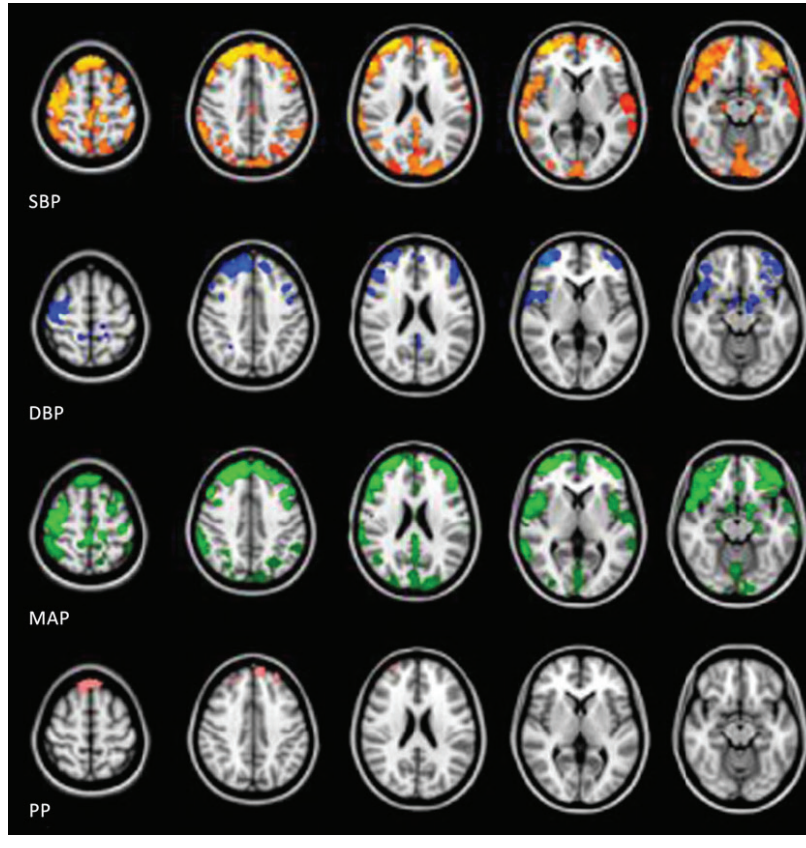

FIGURE 2. Voxel-based analyses of the relationship between blood pressure measures and cortical grey matter magnetization transfer ratio (MTR).
Results are projected on the MNI152 standard space image. Areas show statistically significant associations (P<0.05) of lower blood pressure with a decrease in grey matter MTR (adjusted for age and sex). SBP indicates systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure.

Discussion

In older persons with mild cognitive impairment using antihypertensive medication, BP measures were not associated with WMHs, lacunar infarcts, or microbleeds. However, significant associations were present for SBP, DBP, and MAP with MTR peak height, mean and/or radial diffusivity, and MTR in cortical grey matter, indicating that lower BP was associated with poorer grey matter microstructural integrity.

In line with our results, results of the Rotterdam Scan Study showed no association of increasing SBP or DBP with increasing WMH in persons older than 74 years, whereas in persons up to 74 years such associations existed.[1;22] Even though data from the Framingham

Heart Study showed an association of increasing SBP and DBP with accumulating white matter microstructural damage in healthy young adults,[21] and it has been shown that in middle-aged persons with signs of small vessel disease, a linear relationship between SBP and DBP levels (per 10 mm Hg) and white matter microstructural damage was present.[18] Our data indicate that, besides no associations of BP with manifest vascular white matter damage, more sensitive techniques to pick up ischemic changes, DTI and MTI, did not reveal any association of BP (SBP, DBP, MAP or PP) with white matter damage.

In contrast, our data show that BP measures were mainly associated with grey matter integrity. Rather than higher BP, lower SBP, DBP, and MAP were all associated with grey matter tissue damage, reflected by the lower MTR peak height values, higher MD and RD in grey matter, and lower MTR in cortical grey matter. No associations were found between BP measures and FA and AxD, as these predominantly represent axonal and myelin integrity in the white matter related to preferred diffusion directionality. The MD and RD parameters are indicators for both white and grey matter microstructure, and it has been suggested that these are higher in damaged grey matter tissue as a result of increased free diffusion.[41-43]

The findings of lower BP with subtle grey matter damage fit the observation of the diminished or even reversed detrimental effect of elevated BP in older persons. It is plausible that in our study population of older persons with hypertension, cerebral autoregulation has become impaired by arteriosclerotic damage in such a way that it no longer compensates for reduced cerebral blood flow. While previous studies have shown that white matter is more sensitive than grey matter for hypoperfusion,[44] our data in a sample of older persons with hypertension show that grey rather than white matter integrity is associated with low BP, indicating that there may be a difference in hemodynamic physiology between grey and white matter. On the other hand, a second explanation for our findings we cannot exclude the possibility that lower grey matter microstructural integrity may have been the cause rather than the consequence of low BP and cerebrovascular homeostasis.

The stringent selection criteria resulted in a group of relatively healthy older people, which limits the generalizability of our findings. In addition, due to the cross-sectional design of our study, no causal inference can be made; therefore, future studies are necessary to elucidate whether low BP precedes grey matter integrity in older persons or vice versa.

Our data show that in our population of older persons, lower BP is associated with subtle cerebral ischemic changes specifically in the grey matter. These findings imply that in older persons with mild cognitive dysfunction using antihypertensive medication, not only upper thresholds of BP values, but preferably lower thresholds, should be observed.

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