Determinants of cognitive function in old age

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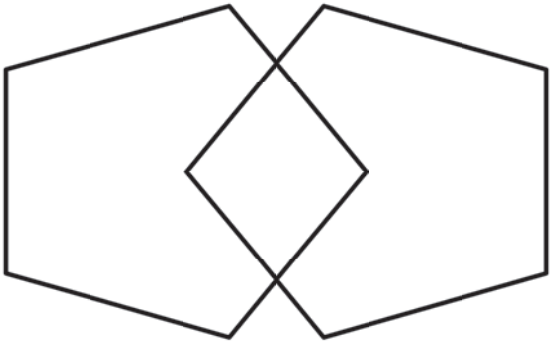
Chapter 3

High blood pressure associates with better cognition in patients with structural brain damage



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Abstract

Introduction

In old age, hypertension is no longer a risk factor for dementia, and higher blood pressures even associate with better cognitive function. We hypothesize that a higher blood pressure is specifically associated with better cognitive function in subjects with structural brain damage.

Materials and methods

In a series of 403 patients who visited the memory outpatient clinic of the Leiden University Medical Center with memory complaints we measured blood pressure, assessed neuropsychological functioning, and performed brain imaging using MRI to determine the amount of grey matter atrophy in an automated matter, and white matter lesion load (WML) semi-quantitatively.

Results

With increasing severity of grey matter atrophy and periventricular WML load, patients were older and had lower MMSE scores (all $p<0.001$). High systolic blood pressure associated with higher MMSE scores, in patients with low normalized grey matter volumes ($p=0.019$) and in patients with severe periventricular WML load ($p=0.031$), but not in patients with medium or high normalized grey matter volumes and patients with moderate or mild periventricular WML load. High systolic blood pressure and high mean arterial pressure also associated with higher CAMCOG-, and WMS-memory quotient scores in patients with low normalized grey matter volumes (all $p<0.025$), but not with Stroop test scores.

Discussion

High blood pressure is associated with better cognitive function in patients with structural brain damage. High blood pressure may be necessary to maintain adequate brain perfusion and function in subjects with structural brain damage.

Introduction

In contrast to hypertension in middle age, high blood pressure in late-life is no longer a risk factor for dementia and has even been associated with a lower risk [1-3]. Moreover, in an 85-year old population it has been shown that higher blood pressure at baseline associated with better cognitive function after five-year follow-up [4]. The pathomechanism behind this age-related reversed relationship is as yet unclear.

A possible explanation is that in old age high blood pressure may be needed to maintain an adequate brain perfusion due to structural and functional changes in cerebral vasculature. Patients diagnosed with dementia have been shown to have a lower cerebral blood flow and more severe cerebrovascular pathology compared to age-matched controls [5,6]. It is still difficult to assess cerebrovascular pathology in vivo, in contrast to the assessment of structural brain damage. Grey matter atrophy and periventricular white matter lesions (WMLs), two commonly used markers of structural brain damage, are both associated with cognitive decline, pre-existent cardiovascular risk factors, and concomitant cerebrovascular pathology [7-11]. We hypothesize that high blood pressure associates with better cognitive function specifically in subjects with strong grey matter atrophy and/or severe periventricular WMLs.

Here, we studied the relation between blood pressure and cognitive function, in strata of grey matter atrophy, and periventricular WML load. We determined blood pressure, the amount of total grey matter atrophy, periventricular WML load, and cognitive functioning in patients with memory complaints, who visited the memory outpatient clinic of the Leiden University Medical Center.

Materials and methods

Participants

Between December 1, 1998, and November 29, 2005, a consecutive series of 600 patients visited the memory outpatient clinic of the Leiden University Medical Center because of memory complaints. Patients were examined according to a standardized protocol. In a multi-disciplinary setting these patients underwent consultation by a medical doctor and/or a neurologist with a general medical and neurological examination, extensive neuropsychological testing, and structural brain imaging using MRI. Cognitive testing took place prior or after MRI testing with a maximal interval of 14 days. Each case was discussed during a weekly consensus meeting, which was formed by representatives of the departments of geriatric medicine, neurology, psychiatry, and neuropsychology. The Medical Ethical Committee of the Leiden University Medical Center approved the study and informed consent was obtained from all patients.

Neuropsychological assessment

Cognitive functioning of all patients was assessed using a standardized neuropsychological test battery. Global cognitive function was assessed with the Mini-Mental State Examination (MMSE) [12], which is incorporated in the Cambridge Cognitive Examination (CAMCOG) [13]. Higher scores indicate better cognitive performance. Memory function was assessed using the Wechsler Memory Scale, which yielded a memory quotient (WMS-MQ), with higher scores indicating better memory function [14]. Executive functioning was assessed using the third chart of the 40-item Stroop test, resulting in the time needed to perform the test [15].

MR data acquisition

Magnetic resonance images were acquired according to a pre-specified scanning protocol for research purposes on a 1.5T MR system (Philips Medical Systems, Best, The Netherlands). T1-weighted 3D gradient echo [120 coronal slices; slice thickness 3 mm; overlap 1.5 mm; TR/TE (ms) 30/4.6; flip angle = 30°; field of view = 220 mm; matrix 256 x 256, reconstruction matrix 512 x512], dual fast spin-echo [48 axial slices; slice thickness; no gap; TR/TE (ms) 3000/27/120; flip angle = 90°; field of view = 220 mm; matrix 256 x 256], and fast fluid attenuated inversion recovery (FLAIR) [22 axial slices; slice thickness = 6 mm; no gap; TR/TE/TI (ms) 8000/100/2000; flip angle = 90°, field of view = 220 mm; matrix 256 x256] sequences were obtained. The line through the inferior border of the genu and splenium of the corpus callosum defined the direction of scanning for the dual echo and FLAIR images. The direction

of scanning for the T1-weighted sequence was perpendicular to this line. MR-scans were not available for use in this study for patients with a contraindication for MR-scanning, who were already scanned in a different hospital, were scanned according to a different protocol, or on a 3T scanner, and for patients whose scans could not be retrieved.

Image post-processing

The degree of grey matter atrophy was measured by estimating grey matter volume, normalized for patient head size, with SIENAX [16], part of FSL [17]. SIENAX starts by extracting brain and skull images from the single whole-head input data, using a T1-weighted scan [18]. The brain image is then affine-registered to MNI-152 space (using the skull image to determine the registration scaling) [19], in order to obtain a volumetric scaling factor, which is used as a normalization for head size. Next, tissue-type segmentation with partial volume estimation is carried out [20] in order to calculate both grey matter and peripheral grey matter volume. All SIENAX processed scans were manually checked for errors in registration and segmentation. Scans with insurmountable errors were removed.

White matter lesion load rating

White matter lesion (WML) load was analyzed for load and location, using T2- and FLAIR sequences. A semi-quantitatively rating scale previously described [21] was used to determine severity of periventricular WMLs and total subcortical WML volume. WMLs were considered present in cases of hyperintense lesions on both T2-weigthed and FLAIR images. Peripheral hyperintense lesions around a hypointense lesion on FLAIR were considered (lacunar) infarcts, and were not included as WMLs. When the largest diameter of a WML was adjacent to the ventricle, it was defined as periventricular, otherwise as subcortical. Periventricular WMLs were rated as 0 (none), 1 (pencil-thin lines and/or caps), 2 (smooth haloes), or 3 (large confluent) for three separate regions; adjacent to the frontal horns, adjacent to the wall of the lateral ventricles, and adjacent to the occipital horns, for both ventricles. Severity of periventricular WMLs was rated as severe (any rate of 3), moderate (any rate of 2), or mild (exclusively rates of 0 or 1). Subcortical WMLs were categorized, according to their maximum diameter, as small (1-3 mm), medium (3-10 mm), or large (>10 mm). Total subcortical WML volume was calculated by assuming subcortical WMLs to be spherical with diameters of 2, 6, or 12 mm and adding up the volumes. Three categories of subcortical WML volume load were used; <100 mm^3, 100-400 mm^3, and >400 mm^3. WML rating was done by the principle investigator (PvV), who was unaware of the clinical information of the patients. Intra-rater and inter-rater

reproducibility was tested in 50 randomly selected patients (by PvV and JvdG). For periventricular WML severity weighted $\varkappa$ value for intra-reader agreement was 0.88 and for inter-reader agreement it was 0.77. Intra-reader correlation coefficient for subcortical WML volume was 0.95 and inter-reader correlation coefficient was 0.93.

Blood pressure

Information on blood pressures was obtained from the clinical data described in the physician letter. Blood pressure was measured using a mercury sphygmomanometer. The systolic value was measured at the onset of phase 1, and the diastolic value was measured at the onset of phase 5 of the Korotkoff sounds. Mean arterial pressure was calculated using the following formula: mean arterial pressure = (systolic blood pressure + (2 * diastolic blood pressure)) / 3.

Statistical analyses

Baseline data are presented as numbers and percentages, means and standard deviations, and median and interquartiled ranges when appropriate. The associations of tertiles of normalized grey matter volume and categories of periventricular WML load with age, MMSE score, and blood pressure were assessed using linear regression analysis. The difference in sex distribution amongst the tertiles and categories was tested using Chi^2-test.

Linear mixed models were used to estimate age-adjusted means of MMSE score for nine categories, which were formed by sex-specific tertiles of systolic blood pressure and normalized grey matter volume, and for nine categories, which were formed by sex-specific tertiles of systolic blood pressure and three categories of periventricular WML load. The interaction between continuous measurements of systolic blood pressure and normalized grey matter volume in relation to MMSE scores was tested using linear regression analysis. A similar strategy was used with other neurocognitive test scores as dependent variables.

All calculations were performed using SPSS software (version 16.0, SPSS Inc, Chicago, Ill).

Figure 1. **Study flow diagram.**

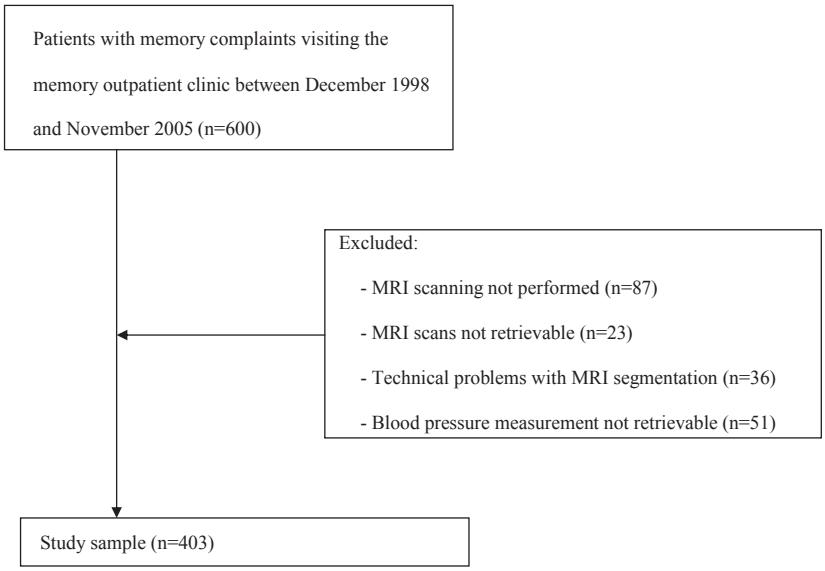


Table 1. **Baseline characteristics of the study patients.**

Total number (n)	403
Men	214 (53%)
Age (years) [a]	70.1 (10.3)
Cognitive function	
MMSE (points) [b]	25 (21-28)
CAMCOG (points) [b]	82 (69-93)
WMS - memory quotient (points) [a]	98.6 (21.2)
Stroop (seconds) [b]	136 (104-186)
Systolic blood pressure (mmHg) [a]	147.9 (22.3)
Diastolic blood pressure (mmHg) [a]	83.4 (10.6)
Mean arterial pressure (mmHg) [a]	104.9 (13.1)
Normalized grey matter volume (L) [a]	0.74 (0.10)
Periventricular white matter lesion severity (n=399)	
Mild	190 (48%)
Moderate	169 (42%)
Severe	40 (10%)
Subcortical white matter lesion volume (n=396)	
<100 mm^3	154 (39%)
100 - 400 mm^3	124 (31%)
>400 mm^3	118 (30%)

[a] Normally distributed continuous variables are presented as means with standard deviations.
[b] Not normally distributed continuous variables are presented as medians with interquartile ranges.

Results

A total number of 403 patients visiting the memory outpatient clinic had complete MRI- and blood pressure measurements available and were eligible for the current study (figure 1). Baseline characteristics of the 403 study patients are shown in table 1.

As is shown in table 2, with increasing severity of grey matter atrophy, reflected by lower normalized grey matter volumes, patients were older and had lower MMSE scores. Patients were also older and had lower MMSE scores with increasing severity of periventricular WML load. Both grey matter atrophy and periventricular WML load associated with systolic blood pressure, but this association disappeared for grey matter atrophy after correction for age ($p=0.468$), whereas it stayed for periventricular WML load ($p=0.012$). Mean arterial pressure also associated with periventricular WML load after correction for age ($p=0.014$). Subcortical WML load did not associate with MMSE score and blood pressure after correction for age (all $p>0.200$) and was subsequently left out of further analyses.

In our main analyses, we tested for the association between blood pressure and cognitive function in strata of grey matter atrophy and strata of periventricular WML load. Figure 2a shows that high systolic blood pressure was associated with higher MMSE scores in patients with low normalized grey matter volumes, whereas this association was absent in patients with medium or high normalized grey matter volumes. Moreover, high systolic blood pressure was also associated with higher MMSE scores in patients with severe periventricular WMLs, but not in patients with moderate or mild periventricular WMLs (figure 2b). The association between systolic blood pressure and MMSE score was also dependent on normalized grey matter volumes when analyses were performed using systolic blood pressure and normalized grey matter volume as continuous variables in a linear model (p for interaction: 0.016, adjusted for sex and age). Comparable results were obtained when using mean arterial pressure and diastolic blood pressure in the models, although the latter failed to reach statistical significance (p for interaction mean arterial pressure: 0.021; p for interaction diastolic blood pressure: 0.081). Similar analyses with the categorical variable 'periventricular WML load' in a linear model with systolic blood pressure did not show statistical significance ($p=0.674$).

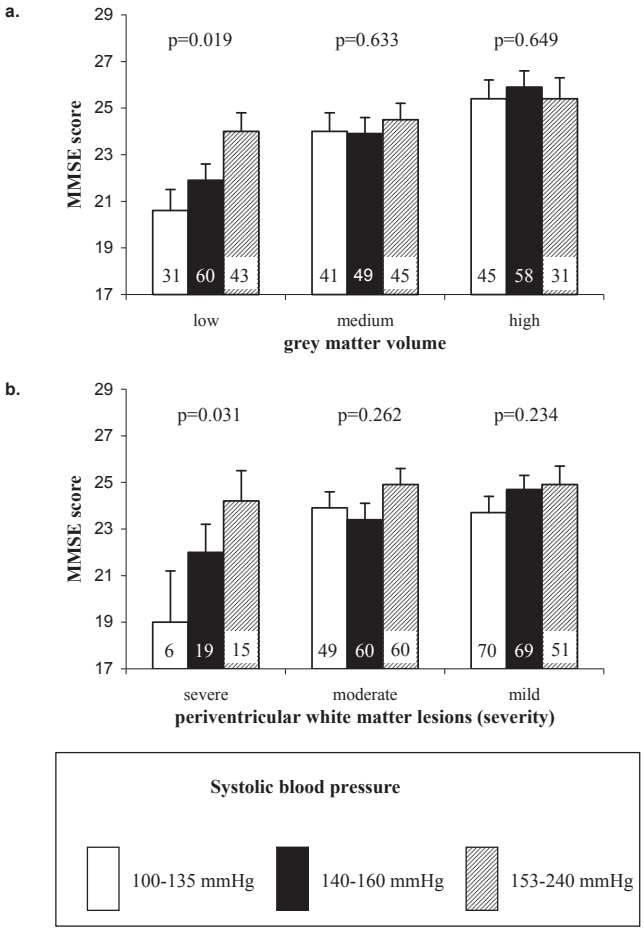
Finally, we tested whether associations of systolic, diastolic blood pressure and mean arterial pressure with cognitive function were also dependent on grey matter atrophy and periventricular WML load for different domains of cognition. Table 3 shows

Table 2. **Sex, age, global cognitive function, and blood pressure dependent on tertiles of grey matter volume and categories of periventricular white matter lesion load.**

Parameters	Tertiles of normalized grey matter volume				Periventricular white matter lesion load			
	Low n=134	Medium n=135	High n=134	p-value	Severe n=40	Moderate n=169	Mild n=190	p-value
Men (%)	69 (52%)	74 (55%)	71 (53%)	0.861*[1]	22 (55%)	79 (47%)	111 (58%)	0.084*[1]
Age, years (95% CI)	74.1 (72.5 – 75.7)	71.8 (70.2 – 73.4)	64.3 (62.7 – 65.9)	<0.001*[2]	75.3 (72.5 – 78.2)	74.1 (72.7 – 75.5)	65.3 (64.0 – 66.6)	<0.001*[2]
MMSE, points (95% CI)	21.8 (21.0 – 22.7)	23.9 (23.0 – 24.8)	26.3 (25.4 – 27.2)	<0.001*[2]	21.7 (20.1 – 23.3)	23.5 (22.7 – 24.3)	25.1 (24.4 – 25.9)	<0.001*[2]
SBP, mmHg (95% CI)	150.5 (146.7 – 154.3)	148.4 (144.7 – 152.2)	144.9 (141.1 – 148.7)	0.039*[2]	156.1 (149.3 – 162.9)	150.3 (146.9 – 153.6)	143.8 (140.7 – 147.0)	<0.001*[2]
DBP, mmHg (95% CI)	83.1 (81.3 – 84.9)	83.9 (82.1 – 85.7)	83.1 (81.3 – 84.9)	0.991*[2]	84.6 (81.3 – 87.9)	83.9 (82.3 – 85.6)	82.5 (81.0 – 84.1)	0.149*[2]
MAP, mmHg (95% CI)	105.5 (103.3 – 107.8)	105.4 (103.2 – 107.6)	103.7 (101.5 – 105.9)	0.245*[2]	108.4 (104.4 – 112.4)	106.0 (104.1 – 108.0)	103.0 (101.1 – 104.8)	0.004*[2]

Legend. P-values represent: *[1] the significance of the difference in the distribution of the patients amongst tertiles of grey matter volume and categories of periventricular white matter lesion load, calculated using Chi^2 testing; *[2] the p for trend over the tertiles of grey matter volume and categories of periventricular white matter lesion load, calculated using linear regression analysis. SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure.

Figure 2. **Global cognitive function dependent on systolic blood pressure, stratified for grey matter volume and periventricular white matter lesion load.**



Tertiles of systolic blood pressure and grey matter volume were created based on the sex-specific medians. Bars and their error bars represent mean MMSE scores with their standard erros, calculated using linear mixed models, adjusted for age. Numbers inside bars represent number of patients. P-values represent the p for trend over the tertiles of systolic blood pressure, calculated using linear regression models, adjusted for age.

that an increase in systolic blood pressure and mean arterial pressure was associated with higher MMSE-, CAMCOG-, and WMS-memory quotient scores in patients with low normalized grey matter volume, whereas the association was absent in patients with medium and high normalized grey matter volumes. Results for diastolic blood pressure showed comparable results, although not significant. Blood pressure did not associate with Stroop-test scores in any of the strata of normalized grey matter

volume. When studying the associations in strata of periventricular WML load, high systolic blood pressure and high mean arterial blood pressure associated with higher MMSE scores and, for mean arterial pressure, with higher CAMCOG scores in subjects with severe periventricular WML load, but not in subjects with moderate or mild periventricular WML load (table 4). No significant associations were found with WMS-memory quotient scores as outcome, although comparable results were observed for systolic blood pressure and mean arterial pressure. Blood pressure did not associate with Stroop-test scores in any of the strata of periventricular WML load.

Table 3. **Cognitive function dependent on blood pressure, stratified for tertiles of grey matter volume.**

Cognitive tests	Blood pressure	Change in test score per 10 mmHg increase in blood pressure			
		Low GM volume	Medium GM volume	High GM volume	p for interaction
MMSE	Systolic	+0.6 (0.2 to 1.0)*	+0.1 (-0.3 to 0.4)	+0.1 (-0.2 to 0.4)	**0.016**
	Diastolic	+0.9 (-0.0 to 1.9)	+0.2 (-0.5 to 1.0)	-0.2 (-0.9 to 0.4)	0.081
	MAP	+1.1 (0.3 to 1.8)*	+0.3 (-0.3 to 0.9)	+0.0 (-0.6 to 0.5)	**0.021**
CAMCOG	Systolic	+1.7 (0.3 to 3.0)*	-0.1 (-1.3 to 1.2)	+0.2 (-0.8 to 1.2)	**0.024**
	Diastolic	+2.5 (-0.6 to 5.5)	+0.4 (-2.1 to 2.9)	-0.9 (-2.9 to 1.2)	0.066
	MAP	+2.8 (0.3 to 5.2)*	+0.9 (-1.1 to 2.9)	-0.1 (-1.8 to 1.6)	**0.025**
WMS-MQ	Systolic	+1.9 (0.4 to 3.3)*	-0.2 (-1.9 to 1.5)	-0.2 (-1.8 to 1.4)	**0.009**
	Diastolic	+2.9 (-0.4 to 6.2)	-0.4 (-3.8 to 2.9)	-0.4 (-3.7 to 2.9)	0.148
	MAP	+3.4 (0.7 to 6.0)*	+0.5 (-2.3 to 3.2)	-0.3 (-2.9 to 2.4)	**0.025**
Stroop	Systolic	+1.8 (-7.8 to 12.0)	-1.3 (-6.9 to 4.3)	+0.4 (-5.4 to 6.2)	0.576
	Diastolic	-7.3 (-28.2 to 13.6)	-4.8 (-17.2 to 7.6)	+3.0 (-7.7 to 13.6)	0.425
	MAP	-1.6 (-18.4 to 15.2)	-2.1 (-12.4 to 8.3)	+1.9 (-7.0 to 10.8)	0.919

Legend. Tertiles of grey matter volume were created based on the sex-specific medians. Estimates (with their 95% confidence intervals) represent the change in test score per 10 mmHg increase in systolic, diastolic blood pressure, or mean arterial pressure (MAP), adjusted for age, calculated using linear regression analysis. P for interaction represents the significance of the association of the interaction between normalized grey matter volume and blood pressure with the cognitive test scores. * $p<0.050$

Table 4. **Cognitive function dependent on blood pressure, stratified for categories of periventricular white matter lesion load.**

Cognitive tests	Blood pressure	Change in test score per 10 mmHg increase in blood pressure			
		Severe pvWML load	Moderate pvWML load	Mild pvWML load	p for interaction
MMSE	Systolic	+0.7 (0.0 to 1.3)*	+0.2 (-0.2 to 0.5)	+0.3 (-0.1 to 0.7)	0.674
	Diastolic	+0.9 (-0.7 to 2.6)	+0.3 (-0.4 to 1.0)	+0.3 (-0.4 to 1.0)	0.691
	MAP	+1.2 (-0.0 to 2.4)	+0.3 (-0.3 to 0.9)	+0.4 (-0.2 to 1.0)	0.580
CAMCOG	Systolic	+2.5 (0.6 to 4.5)*	+0.4 (-0.7 to 1.4)	+0.7 (-0.5 to 2.0)	0.430
	Diastolic	+2.5 (-2.8 to 7.7)	+0.7 (-1.5 to 2.9)	+0.7 (-1.6 to 3.0)	0.687
	MAP	+4.1 (0.2 to 8.0)*	+0.7 (-1.0 to 2.5)	+1.0 (-1.0 to 2.9)	0.317
WMS-MQ	Systolic	+2.2 (-0.3 to 4.8)	+0.5 (-0.9 to 1.8)	+0.5 (-1.1 to 2.0)	0.325
	Diastolic	+1.9 (-4.7 to 8.4)	+1.2 (-1.6 to 3.9)	-0.1 (-3.1 to 2.9)	0.498
	MAP	+3.4 (-1.6 to 8.5)	+1.0 (-1.3 to 3.2)	+0.4 (-2.2 to 2.9)	0.317
Stroop	Systolic	+1.0 (-6.7 to 8.6)	+1.4 (-5.6 to 8.4)	+1.8 (-3.6 to 7.2)	0.870
	Diastolic	-10.6 (-30.6 to 9.5)	-2.8 (-17.1 to 11.6)	-0.3 (-11.2 to 10.6)	0.556
	MAP	-2.3 (-17.4 to 12.8)	-0.0 (-11.7 to 11.6)	+1.6 (-7.3 to 10.4)	0.717

Legend. Estimates (with their 95% confidence intervals) represent the change in test score per 10 mmHg increase in systolic, diastolic blood pressure, or mean arterial pressure (MAP), adjusted for age, calculated using linear regression analysis. P for interaction represents the significance of the association of the interaction between periventricular white matter lesion (pvWML) load and blood pressure with the cognitive test scores. * $p<0.050$

Discussion

This study shows that high blood pressure associates with better cognitive function in patients with a high degree of grey matter atrophy and in patients with severe periventricular WML load. Blood pressure does not associate with cognitive function in patients with medium or low grey matter atrophy severity and in patients with moderate or mild periventricular WML load. In patients with severe grey matter atrophy and in patients with severe periventricular WML load, high blood pressure associates with better global cognitive function and in large part with better memory function, but not with executive function.

Both high systolic blood pressure and high mean arterial pressure associated with better cognitive function in subjects with grey matter atrophy and severe periventricular

WML load. Because mean arterial pressure gives a good representation of actual perfusion pressure over the cardiac cycle and is the steadier component of blood pressure, as opposed to systolic blood pressure [22], these results lend support to the hypothesis that high blood pressure may be needed to maintain adequate brain perfusion. Moreover, we found this association for two commonly used tests for global cognitive function and memory function separately.

To our knowledge we are the first to report that the association between blood pressure and cognitive function is dependent on the degree of structural brain damage. A positive association between systolic blood pressure and cognitive function has been described before in several large population studies [23,24]. Our results are partly in agreement with these studies, but here we show that this association is primarily driven by the presence of severe grey matter atrophy and/or severe periventricular WMLs.

Following our results the question arises why high blood pressure associates with better cognitive function in patients with severe structural brain damage. Possibly, high blood pressure is necessary to maintain adequate brain perfusion in subjects with structural brain damage due to changes in, or decreased function of cerebral vasculature. Evidence for this reasoning comes from studies that investigated the role of changes in the cerebral vasculature observed in brains from demented patients. In brain autopsy studies, Alzheimer's disease (AD) brains have been shown to have narrowed cortical microvessels, especially when in proximity of beta-amyloid plaques [25], have a decreased capillary density [26], and have increased beta-amyloid deposition in both large cerebral vessels and capillaries [27]. Together with fibrohyalinic thickening of cerebral vessel walls, caused by longstanding hypertension [28], these changes result in an increased cerebral vascular resistance. Cerebral vascular resistance can also be increased due to a loss of cholinergic activity in the course of AD, since cholinergic neurons have the property to induce cerebral vasodilatation [29]. All together, high blood pressure may be needed to overcome the increased cerebral vascular resistance and this could explain for our findings. When patients are not capable of increasing blood pressure or maintaining high blood pressure the resultant cerebral hypoperfusion may result in, what has been called by others, a neuronal energy crisis [30].

Because our results show that high blood pressure is associated with better cognitive function in patients with structural brain damage, the question arises whether we should refrain from blood pressure lowering in subjects with structural brain damage who have high systolic blood pressure or high mean arterial pressure. This reasoning has already been discussed with respect to antihypertensive treatment in patients

with coronary artery disease, and in patients with acute ischemic stroke [31,32]. With increasing reduction of (diastolic) blood pressure in patients with coronary artery disease, the risk of all-cause death and myocardial infarction has been shown to increase, and preliminary results have shown that post-stroke induced hypertension might result in neurological improvement. In combination with results from a study that has shown low blood pressures to associate with accelerated decline of renal function in old age [33], this hints to better organ perfusion with higher blood pressures. Hypothetically, based on these and our results, discontinuation of antihypertensive treatment in patients with structural brain damage could result in better brain perfusion and subsequently halt or even reverse cognitive decline due to increasing blood pressure. Objecting this hypothesis are results from the Syst-Eur trial in which antihypertensive treatment was shown to reduce the risk of dementia [34] and from the HYVET-study which showed that antihypertensive treatment of an elderly population did not change the risk of dementia [35]. However, the beneficial effect on the risk of dementia in the Syst-Eur trial might well be explained by the calcium antagonistic effect and not the blood pressure lowering effect, as has been suggested following the results from an observational study [36]. Moreover, in both studies, the presence of dementia at baseline was an exclusion criterion, and therefore, the number of participants with severe structural brain damage was supposedly low. Although treatment of high blood pressure in patients with structural brain damage may have negative implications for cognitive function, future research should first be focused on investigating the effect of blood pressure variation on brain perfusion and cerebral capillary resistance, before intervention studies can be designed and performed.

A limitation of this study is the cross-sectional character of the study design and data acquisition. This makes it hard to study the route of biological and causal pathways underlying the found associations. However, by stratifying our analyses for structural brain damage severity we were able to answer the question whether blood pressure is specifically positively associated with cognitive function in patients with severe structural brain damage, which underlies a plausible biological explanation.
A strong point of this study is the availability of a large population of patients with large variations in cognitive function, grey matter atrophy severity, and periventricular WML load, which allowed us to study our hypothesis. Another strong point is that the neuropsychological test battery allowed us to study the associations between blood pressure and specific domains of cognitive function.
In conclusion, we showed that high blood pressure is associated with better cognitive function in patients with severe structural brain damage. High blood pressure may be necessary to maintain adequate brain perfusion and function in subjects with structural brain damage.

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