

BP, Brain, and Cognition

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Blood pressure, brain structure, and cognition: opposite associations in men and women

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ABSTRACT

Background: Research on associations between blood pressure, brain structure and cognitive function has produced somewhat inconsistent results. In part, this may be due to differences in age ranges studied and to sex differences in physiology and/or exposure to risk factors which may lead to different time-course or patterns in cardiovascular disease progression. The aim of this study was to investigate the impact of sex on associations between blood pressure, regional cerebral volumes, and cognitive function in older individuals. **Methods:** In this cohort study, brachial blood pressure was measured twice at rest in 266 community-based individuals free of dementia aged 68-73 years who had also undergone an MRI scan and a neuropsychological assessment. Associations between mean blood pressure (MAP), regional brain volumes, and cognition were investigated with voxel-wise regression analyses. **Results:** Positive associations between MAP and regional volumes were detected in men while negative associations were found in women. Similarly, there were sex differences in the brain-volume cognition relationship with a positive relationship between regional brain volumes associated with MAP in men and a negative relationship in women. **Conclusions:** In this cohort of older individuals higher MAP was associated with larger regional volume and better cognition in men while opposite findings were demonstrated in women. These effects may be due to different life-time risk exposure or to physiological differences between men and women. Future studies investigating the relationship between blood pressure and brain structure or cognitive function should evaluate the potential for differential sex effects.

Keywords: mean arterial pressure, brain structure, cognitive function, epidemiology, sex

Systemic hypertension is a promoter of adverse cerebrovascular events and reduced cognitive function. Individuals with higher systolic and diastolic blood pressure in mid-life and early old-age have a two to five-fold increased risk of stroke ¹, a 50% increased risk of vascular dementia ², and there is evidence that mid-life blood pressure (BP) is associated with the development of amyloid angiopathy ³. Associations between hypertension, lacunar infarcts, and presence of white matter lesions in mid- and later-life have also been demonstrated ^{4, 5}. However, in older populations the influence of elevated BP and brain health is less clear. In some studies, lower diastolic BP has been found to be associated with higher risk of mild cognitive dysfunction and dementia ^{6, 7} and lower systolic BP has been associated with a greater risk of cognitive impairment in individuals aged 80 years and older ⁸. In contrast, other studies suggest an ongoing promotion of cerebral pathology and cognitive decline with elevated BP ⁹. A possible mechanism for these conflicting observations is that in individuals with cerebrovascular disease, higher BP levels are required to regulate sufficient blood flow to maintain cerebral function in cerebral regions that may otherwise suffer from chronic hypoperfusion. Consistent with this hypothesis are findings in older individuals aged 60-90 years showing that a decline of more than 10mmHg over a period of 20 years are associated with a greater extent of cortical atrophy ¹⁰.

Confounding factors in this area of research include reporting on varying age ranges and inadequate consideration of possible sex differences. Previous investigations have studied individuals across a large age range and often without considering non-linear effects thus making it difficult to separate BP effects from those of other factors associated with pathological aging. Many studies have also limited their enquiry to brain structure or to cognition, thus limiting their capacity to demonstrate a link between BP levels, brain structure and cerebral function in the

same individuals. In addition, despite the fact that clear sex differences in genetic predisposition and risk factor profiles have been identified¹¹ past research has often either focused on one sex or has failed to stratify analyses for this factor thus somewhat obscuring sex effects. Consequently, the aim of this study was to investigate the associations between BP, brain structure, and cerebral function while scrutinising sex difference, in a large cohort of generally healthy community-living older individuals.

Prior research has demonstrated that the relative strength of association between systolic and diastolic BP and CVD risk fluctuates with age¹², and cerebral perfusion is more dependent on mean arterial blood pressure (MAP) than systolic or diastolic blood pressure alone (as demonstrated in some critical care settings)¹³. Moreover, as we have previously demonstrated an association between lower diastolic BP, BP lowering medication, and an increased risk of mild cognitive impairment in the parent study from which the present imaging cohort has been selected⁶, we hypothesised that higher MAP would be associated with greater regional grey matter volumes and that brain regions associated with MAP would be positively associated with cognitive function

RESEARCH DESIGN AND METHODS

Subjects

Participants were sampled from the Personality and Total Health Through Life (PATH) project, a large longitudinal study designed to investigate the course of mood disorders, cognition, health and other individual characteristics across the adult lifespan¹⁴. It comprises 7485 individuals in three age groups of 20-24, 40-44 and 60-64 years at baseline with follow-up assessments every four years. PATH includes residents of the city of Canberra and the adjacent town of Queanbeyan, Australia, who were randomly recruited through the electoral roll¹⁴. As

enrolment to vote is compulsory for Australian citizens, this cohort is representative of the general population. The study was approved by the Australian National University Human Research Ethics Committee.

The present investigation is focused on the older participants (60's cohort) at the third assessment, approximately 8 years after wave 1. Of the 2551 randomly selected into the 60s cohort at wave 1, 2076 consented to be contacted regarding an MRI scan. Of the randomly selected subsample of 622 subjects that was offered an MRI scan at baseline, 478 (77%) eventually completed MRI scanning and 360 participants were rescanned at wave 3. For this study, we excluded 94 (26.1%) subjects with gross brain abnormalities ($n = 18$); a history of epilepsy, Parkinson's disease or stroke ($n = 30$); or mild cognitive impairment or dementia evident on clinical and neuropsychological assessment (see ¹⁵ for a detailed description) meeting clinical criteria ($n = 46$). The study sample ($n = 266$) did not differ from the larger PATH sample on sex (women 45.9% vs. 48.4%, ns), but had completed more years of education (14.3 vs. 13.7; $p < 0.01$).

Socio-demographic and health measures

Socio-demographic and health information including race, years of education, alcohol consumption, smoking and depression were assessed by self-report. Body mass index (BMI) was based on participants' self-report of weight and height and computed using the formula weight (kg)/height(m)². The Alcohol Use Disorder Identification Test (AUDIT) was used to assess alcohol intake ¹⁶. For men, weekly alcohol consumption was categorized as light (1–13 units), moderate (14–27 units), hazardous (28–42 units) or harmful (>42 units). For women, weekly alcohol consumption was divided into light (1–7 units), moderate (8–13 units), hazardous (14–28

units) or harmful (>28 units) categories where a unit equates 10g of pure alcohol ¹⁷.

Blood pressure measure

Brachial BP (upper arm) was measured twice with an Omron M4 monitor using an appropriately sized cuff in a seated position after a period of resting for at least 5 minutes. MAP was computed with the formula $\text{MAP (mmHg)} = \text{diastolic BP} + (1/3 * (\text{systolic BP} - \text{diastolic BP}))$. Participants were classified as hypertensive if they were on medical therapy for hypertension or if they had an average systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg.

Cognitive assessment

Verbal working memory was assessed through the Digits-Backwards Span test (DB) - a subtest of the Wechsler memory scale ¹⁸. Lexical knowledge was assessed using the Spot-the-Word test (STW) ¹⁹. Episodic memory was assessed on the first trial of the California Verbal Learning Test for both immediate (IR) and delayed (DR) recall ²⁰. The Boston Naming Test (BNT) ²¹ was used to assess language function. Verbal fluency was assessed using the Controlled Oral Word Association Test (COWAT) A and F-words. Perceptual motor ability and manual dexterity were assessed using the Purdue Pegboard Test (PP) ²². Processing speed and executive function, i.e. cognitive flexibility, frontal lobe function, were assessed using the Symbol Digit Modalities Test ²³ (SDMT) and with the Trail Making Test A and B (TMT-A/B) ²⁴. For all tests, higher scores represented better performance except for the Purdue Pegboard Test and the Trail Making Tests where higher scores reflected slower motor and processing speeds and hence lower performance.

Data Acquisition

Subjects were scanned on a Siemens Avanto scanner (Siemens Medical Solutions) for T1-weighted three-dimensional structural MRI. The T1 weighted MRI was acquired in sagittal orientation using the following parameters: repetition time (TR)/echo time (TE) = 1.16/0.8 ms; flip angle = 15°; matrix size = 512 X 512; slice thickness = 1.0 mm; resulting in a final voxel size of 1x1x1.

Image Processing and Analyses

All images were pre-processed using the MINC imaging toolbox (MINC; <http://en.wikibooks.org/wiki/MINC>). Images underwent automatic QC to identify outliers via image histogram clamping and comparisons to the group minimum deformation average ²⁵. Images were then B0 MRI inhomogeneity corrected using N3 ²⁶, and normalised via a linear correction to a global intensity model ²⁵.

Statistical analysis of relationship between blood pressure and regional brain volumes

Optimized voxel-wise analyses were conducted using Statistical Parametric Mapping 8 (SPM8; Wellcome Department of Cognitive Neurology, London, UK, 2003) on Matlab 7.12 (Math Works, Natick, MA, USA, 2002), stratified by sex. Images were first segmented into grey matter, white matter and cerebrospinal fluid ²⁷. Grey and white matter segmentations were further normalized to the sample template (population representative) which was generated by the diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) algorithm from participants' complete images ²⁸. Images were smoothed using a 8-mm, full-width-at-half-maximum Gaussian kernel to increase the signal-to-noise ratio, with each voxel of

the resulting grey matter images representing the absolute amount of grey matter volume equivalent to their volume per unit before normalization²⁹.

Absolute total grey matter volumes were calculated using the native space grey matter segmentations. Smoothed grey matter density images were used in the voxel-wise regression analyses with MAP as predictor and controlling for age, sex, BMI, depression and alcohol consumption. This type of analysis is equivalent to conducting a multiple regression analysis at each voxel occupied by brain tissue and displaying results in three-dimensional space (see below) after applying a more stringent statistical threshold to account for multiple analyses. Alpha was set at $p < 0.00005$.

Statistical Analysis of Volume-Cognition Relationships

Group characteristic analyses were conducted using IBM SPSS Statistics 20. Grey matter densities at significant voxels were extracted and standardized to Z-scores. Due to the nonparametric distribution of cognitive test performance, Spearman's Rank Order correlations were used to assess the association between the BP-related cluster volumes and cognitive function, stratifying for sex. Missing data for cognitive measures and covariates were imputed using the EM algorithm (<1% of all variables and <2% for any one variable). Alpha was set at $p < 0.05$.

RESULTS

The characteristics of the study population are presented in **Table 1**.

Associations between blood pressure and regional brain volumes

Associations between MAP and regional brain volumes in men and women are presented in **Table 2**. Voxelwise analyses using MAP as a predictor while adjusting for age, BMI, depression, smoking, diabetes and alcohol consumption showed that in men, higher MAP is associated with **larger** regional grey matter volumes, specifically in the regions of the right superior frontal gyrus, right middle temporal gyrus, right lingual gyrus and left posterior cingulate gyrus. In contrast, higher MAP in women is associated with **smaller** regional grey matter volumes in the left medial superior frontal gyrus. These results not only show that different regions are associated with MAP in men and women (**Figure 1**), but also that the direction of association followed opposite directions in men and women with a positive association in men and a negative association in women. Additional voxelwise analyses were conducted to determine whether associations between MAP and regional grey matter volumes were driven predominantly by diastolic or systolic BP. In men, they revealed that diastolic (but not systolic) BP was positively associated with regional grey matter (**Figure 1**) for regions in which volumes were influenced by MAP as well as additional regions including the right superior frontal gyrus, left inferior temporal gyrus, right middle temporal gyrus, right precentral gyrus, left and right parietal lobe, left and right precuneus; and right uncus. No significant association was detected in women.

To investigate a possible effect of antihypertensive medication scatter plots graphing MAP against regional brain volumes were produced for regions in which volumes were influenced by MAP, stratified for three groups: those with no hypertension, those with hypertension who were not on antihypertensive medication, and those with hypertension on antihypertensive therapy. **Figure 2** shows graphs of the superior frontal cortex and indicates that MAP is associated with larger volumes in men and smaller volumes in women, in each medication group. Associations

for other regions identified in men only are presented in **Supplementary Figure 1**. Post-hoc tests confirmed that associations did not differ between groups for men or women ($p>0.05$) for any of the regions of interest.

Volume-Cognition Relationships

In men, grey matter densities in the right lingual gyrus (Region 3) were positively associated with memory (IR: $\rho=0.27$, $p<0.01$) and language function (BNT: $\rho=0.24$, $p<0.01$) scores (**Supplementary Table 1**). In women, grey matter densities in the left medial superior frontal gyrus (Region A) were negatively associated with memory (IR: $\rho=-0.21$, $p=0.02$; DR: $\rho=-0.24$, $p<0.01$) scores. No associations were tested between white matter volumes and cognitive function in women as no regional volumes were identified to be associated with MAP. Significant associations between MAP and cognition were found in men only for immediate recall ($\rho=0.21$, $p<0.05$) and delayed recall ($\rho=0.17$, $p<0.05$) (see **Supplementary Table 2**).

Pulse pressure contribution

To further characterize the associations between MAP and grey matter volumes and to satisfy a reviewer's request we conducted further analyses testing possible effects (either as predictor or as covariate) of pulse pressure (PP) as an index of stiffness of large arteries. None of the analyses investigating PP as predictor of grey matter volume produced significant results. When testing the association between MAP and regional volumes stronger results (i.e. more and larger regions reaching the significance level) were detected indicating, as previously, that higher MAP was associated with larger grey matter volumes (**Supplementary Figure 2**).

MAP, white matter regional volumes and cognition

Although not the focus of this study, additional analyses were conducted to determine whether associations between MAP and white matter volumes were consistent with those detected in grey matter. As for grey matter, white matter was positively associated with MAP in men (**supplementary Table 3**) and also showed consistent association with cognition (**supplementary Table 4**).

DISCUSSION

This study produced three main findings. First, significant associations were found between MAP and regional brain volumes, however, the direction of associations differed according to sex with a positive association between MAP and regional brain volumes in men and a negative association demonstrated in women. Specifically, associations between MAP and regional volumes in men appeared to be prominently driven by DBP rather than SBP. Second, regional brain volumes associated with MAP were positively associated with cognitive function. Finally, the relationship between brain volume and cognition also differed according to sex with a positive association in men and negative association in women.

The positive association between MAP and regional volumes found in men is consistent with previous findings from our cohort showing that higher diastolic BP reduced the risk of conversion from normal aging to mild cognitive disorders ⁶. This pattern is also consistent with prior findings ⁸ showing that higher BP in individuals with atherosclerosis and small vessel disease is associated with better brain health, possibly due to higher BP maintaining cerebral perfusion ^{10, 30}.

In contrast, our findings in women of a negative association between MAP and specific brain regional volumes were unexpected. We were not able to explain the findings in women through the effects of demographic and clinical confounders such as the use of antihypertensive medications. Sensitivity analyses showed that associations between MAP and regional brain volumes did not vary according to whether individuals were normotensive or hypertensive, or whether antihypertensive therapy was instituted. Unmeasured anatomic physiological and genetic confounders ¹¹ such as the effects of central aortic pressure, arterial stiffness or atherosclerotic cerebrovascular disease will need to be explored in future studies.

Of particular interest was our finding that there was a sexual dimorphism in regional brain volume-cognition relationships. In men, structures positively associated with MAP were positively associated with cognition suggesting higher BP may maintain function. Whereas in women, structures negatively associated with MAP were positively associated with cognition suggesting that higher BP is associated with poorer cognitive function.

This study had a number of limitations but also significant strengths. It used a narrow age-cohort and therefore the results detected in this age-group may not apply to other age groups. However, such design is also advantageous as it decreases the effects attributable to birth cohorts (e.g. wars, malnutrition, education, etc.). BP was assessed in a single session (albeit twice) by peripheral measures that are known to be imprecise, vary across time and are potentially affected by the “white coat” effect even though measurements occurred in a non-clinical environment. Non-invasive measure of central BP including central pulse pressure should be tested in future investigations to confirm the present findings. Causal inferences cannot be made due to the cross-sectional research design. Moreover, analyses between structure and function were exploratory and were not adjusted for multiple comparisons.

We conclude that in this cohort, MAP is associated with larger regional brain volumes and better cognition in men, while the opposite is found in women. These effects may be due to different life-time risk exposure in men and women or to physiological differences between the sexes and highlight the importance of stratification by sex in the evaluation of the effects of BP, regional brain volumes and cognition. If confirmed in future studies, our findings may have important clinical implications as to the management of systemic hypertension to maintain cognitive function in our aging population.

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DISCLOSURE

The authors report no conflict of interest

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FIGURES

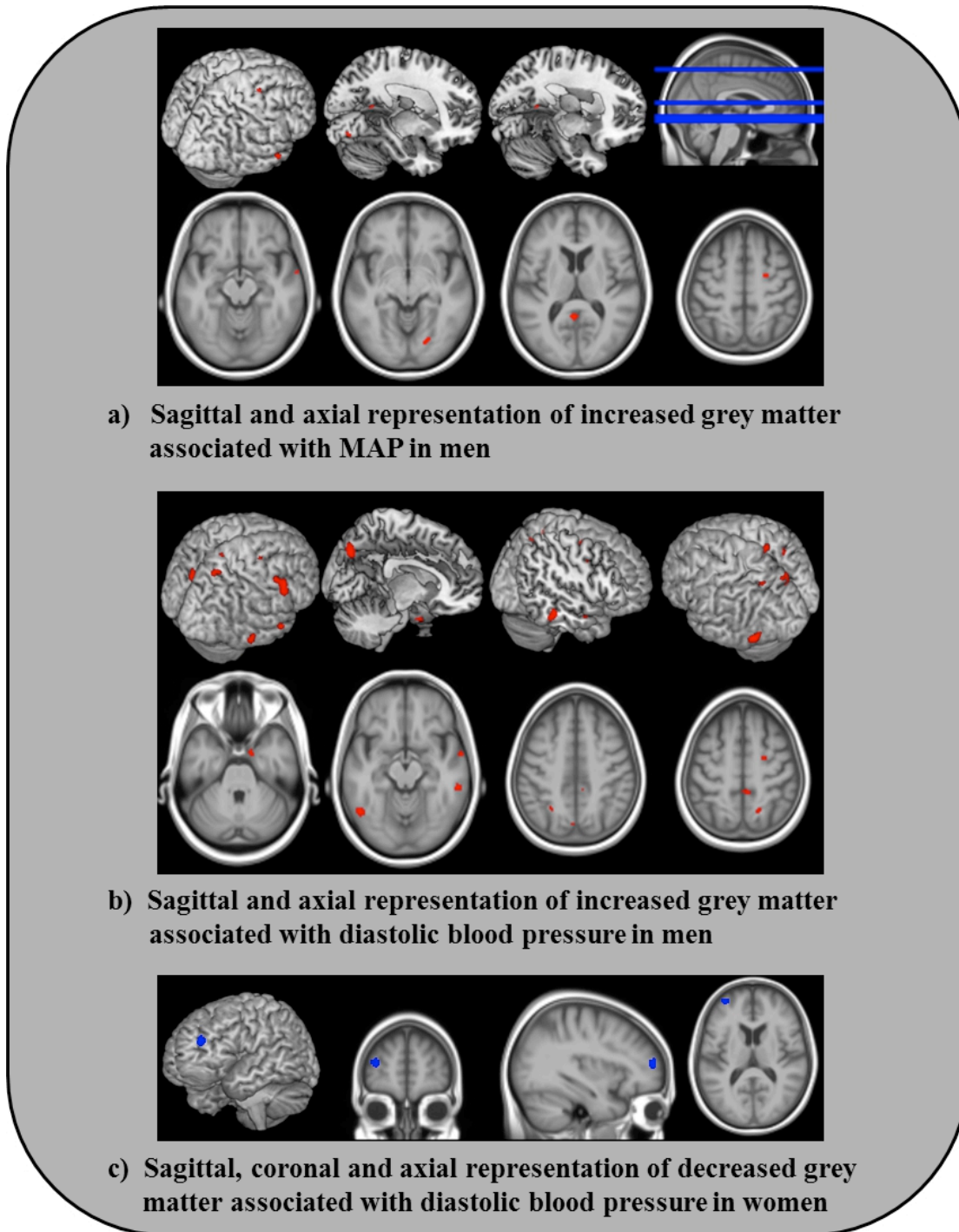


Figure 1. Associations between mean arterial blood pressure (MAP, a/c) and regional grey matter volumes in men and women and between diastolic blood pressure and regional grey matter in men only (b).

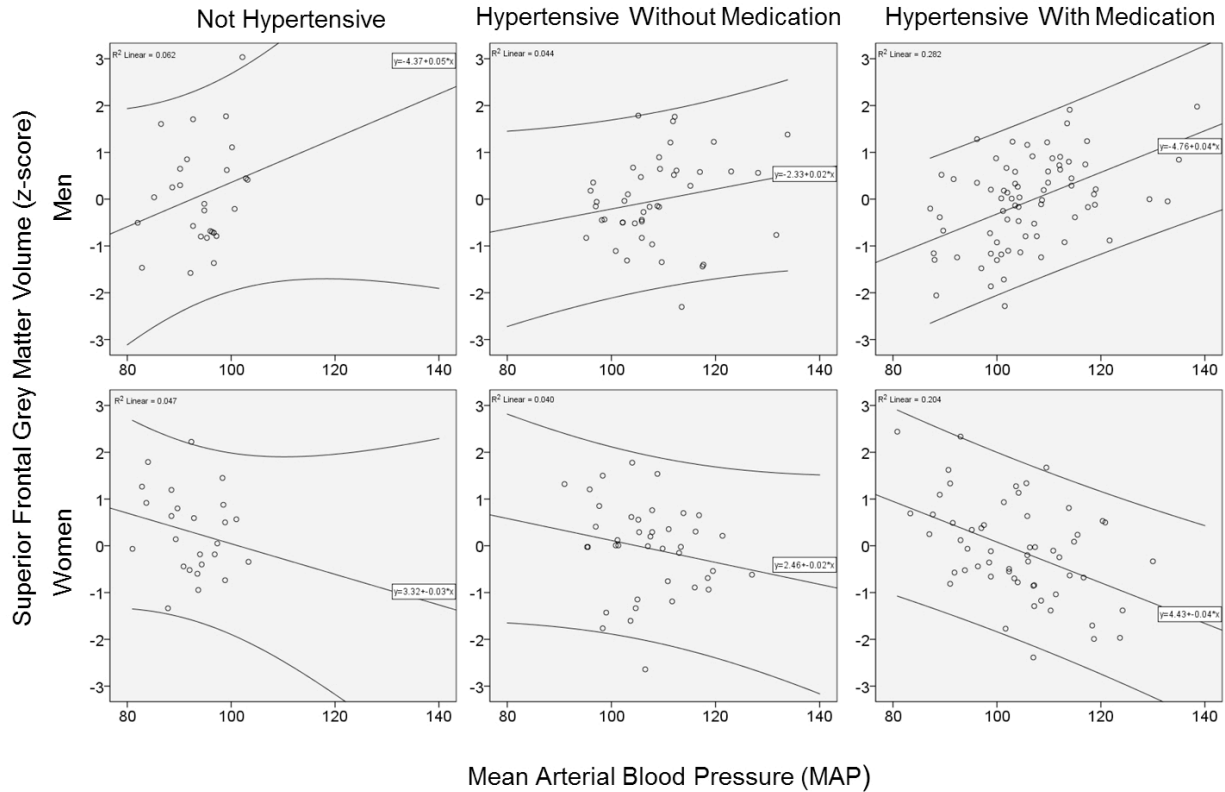


Figure 2. Scatter plots presenting associations between mean arterial blood pressure (MAP) and grey matter volume in the superior frontal gyrus in men (top row) and women (bottom row).

Table 1. Characteristics of the study population.

Characteristics	All (N = 266)	Male (N=144)	Female (N=122)	male vs female, p
Age, years (SD)	70.4 (1.42)	70.4(1.44)	70.4 (1.40)	0.96 [†]
Range	68-73	68-73	68-73	
Caucasian, N (%)	254 (95.5)	137 (95.1)	117 (95.9)	0.42 [‡]
Education, years (SD)	14.20 (2.57)	15.00 (2.27)	13.30 (2.61)	<0.001 [†]
MMSE, score (SD)	29.4 (0.87)	29.3 (0.88)	29.4 (0.86)	0.15 [†]
BMI, score (SD)	26.6 (4.91)	26.5 (3.73)	26.8 (6.02)	0.71 [†]
MAP, mmHg (SD)	103.9 (11.2)	105.0 (11.5)	102.6 (10.7)	0.08 [†]
SBP, mmHg (SD)	149.7 (19.5)	150.3 (19.9)	148.9 (18.9)	0.56 [†]

DBP, mmHg (SD)	81.00 (9.84)	82.40 (10.0)	79.50 (99.4)	0.02 [†]
BP medication, N (%)	131 (49.2)	74 (51.4)	57 (46.7)	0.45 [‡]
Alcohol Consumption				<0.001 [‡]
Abstain/Occasional, N (%)	61 (22.9)	20 (13.9)	41 (33.6)	
Light/Medium, N (%)	164 (61.7)	109 (75.7)	73 (59.8)	
Hazardous/ Harmful, N (%)	20 (7.52)	13 (9.03)	7 (5.74)	
Ever smoker, N (%)	114 (42.9)	70 (48.6)	44 (36.1)	0.04 [‡]
Cognitive Test Performance				
Immediate Recall, mean (SD)	6.89(2.03)	6.47(1.74)	7.40 (2.24)	<0.001 [†]
Delayed Recall, mean (SD)	6.07 (2.18)	5.70 (1.90)	6.50 (2.41)	<0.01 [†]
Digit Backwards, mean (SD)	5.28 (2.03)	5.62 (2.01)	4.88 (1.99)	<0.01 [†]
Spot the Word, mean (SD)	53.50 (5.07)	54.40 (4.55)	52.40 (5.46)	<0.01 [†]
Purdue Pegboard, mean (SD)	12.40 (1.98)	11.90 (2.02)	13.10 (1.73)	<0.001 [†]
Trail Making Test B, mean (SD)	80.0 (29.8)	78.0 (28.1)	82.4 (31.6)	0.23 [†]
COWAT A-words, mean (SD)	12.80 (5.39)	13.30 (5.39)	12.30 (5.38)	0.12 [†]
Boston Naming Test, mean (SD)	13.90 (1.31)	13.90 (1.29)	13.80 (1.34)	0.22 [†]

[†] t-test [‡] chi-square test; BMI: body mass index; MMSE: mini mental state examination; MAP: mean arterial blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure

Table 2: Associations between mean arterial pressure and regional grey matter volumes assessed by voxel-wise regression which revealed positive associations in men and a negative association in women.

	MNI coord. (x, y, z) ¹	Cluster extent (k) ²	Cluster-level P uncorrected ³	Cluster-level Beta ⁴	Region description (for cluster peak) ⁵
Men (positive associations)					
Region 1	22, -4, 54	44	<0.00005	0.352	Right superior frontal
Region 2	64, -1, -14	27	<0.00005	0.352	Right middle temporal
Region 3	21, -76, -6	49	<0.00005	0.373	Right lingual

Region 4	-2, -49, 9	59	<0.00005	0.340	Left posterior cingulate
Women (negative associations)					
Region A	-3, 56, 12	68	<0.00005	-0.394	Left medial superior front.

¹ The coordinate column indicates the location of the significant findings in a standardised space based on the Montreal Neurological Institute (MNI) template used in SPM analyses. ² The cluster extent column indicates the size in voxels of the significant region.

³ The cluster-level column indicates the level of significance at which these findings were tested.

⁴ The cluster-level Beta column indicates the standardised regression coefficient for MAP at the cluster level

⁵ The region description column reports the name of the region identified by the MNI coordinates.