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Higher blood pressure predicts lower regional grey matter volume: Consequences on short-term information processing

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Abstract

Hypertension is a risk factor for diffuse brain atrophy. Yet, there is little evidence that higher blood pressure predicts focal brain atrophy, as indicated by a lower volume of regional brain tissue. This voxel-based morphometry study tested (a) whether higher blood pressure predicts lower regional grey or white matter volume and (b) whether a blood-pressure-related reduction in regional brain tissue volume predicts poorer neuropsychological test performance. Participants were 76 men (M age = 61.33, SD = 4.95 years) and 58 women (M age = 59.86, SD = 5.10 years) without a cardiovascular, cerebrovascular, or neuropsychiatric disease. Results showed that among men, higher resting systolic blood pressure predicted lower grey matter volume in the supplementary motor area and adjacent superior frontal gyrus, the anterior cingulate cortex, and middle temporal gyrus. Among men, lower grey matter volume in the supplementary motor area also predicted a slower time to complete the Trail Making Part B Test of executive control and a poorer recall of items from the Four-word Short-term Memory Test of working memory. These relationships were independent of age, total brain tissue volume, educational history, severity of carotid atherosclerosis, and the extent of periventricular and subcortical white matter lesions. Among women, no statistically significant relationships were found between blood pressure, regional brain tissue volume, and cognitive function. These findings suggest a functional relationship among men between higher blood pressure, lower regional grey matter volume, and poorer cognitive function that is independent of other risk factors and confounding medical conditions.

Keywords

Brain atrophy; Blood pressure; Cognitive function; Grey matter; Voxel-based morphometry

Hypertension is a putative risk factor for neuropathology and diffuse brain atrophy. For example, high midlife systolic blood pressure not only predicts the presence of neuritic plaques in the cortex and hippocampus but also a low brain weight at death (Petrovitch et al., 2000). In vivo evidence from structural magnetic resonance imaging (MRI) studies also indicates that higher blood pressure predicts a greater severity of ischemic white matter lesions and a lower volume of brain tissue (DeCarli et al., 1995, 1999; den Heijer et al., 2003, 2005; Goldstein et al., 2002; Korf et al., 2004; Raz et al., 2003; Salerno et al., 1992; Strassburger et al., 1997; Swan et al., 1998b; Wiseman et al., 2004). These findings in humans parallel those in animal models of high blood pressure and brain structure. For example, overall brain tissue volume and cortical thickness are reduced by 11 to 25% in spontaneously hypertensive rats, as compared with Wistar Kyoto control rats (Tajima et al., 1993). Animal models also indicate that high blood pressure may contribute to neuropathology, brain atrophy, and to other adverse changes in brain structure by restricting cerebral blood flow and by compromising the integrity of the blood–cerebrospinal fluid and blood–brain barriers; both of these pathological changes

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can, in turn, disrupt nutrient delivery to brain tissue and promote cell death (Al-Sarraf and Philip, 2003a,b; Gesztelyi et al., 1993; Kemper et al., 2001; Tajima et al., 1993). It has been speculated that the neuropathology and brain atrophy that result from chronic high blood pressure may impair a range of cognitive functions—particularly executive functions that are supported by regions within the frontal lobes (DeCarli, 2004; DeCarli et al., 2001; Launer et al., 1995, 2000; Moore et al., 2002; Raz et al., 2003; Swan et al., 1998b; Waldstein et al., 1991).

At present, however, there is little converging evidence that higher blood pressure predicts focal atrophy in brain regions that may support the cognitive functions that are often mildly impaired among individuals with hypertension (e.g., executive functions such as behavioral planning and working memory; Elias et al., 1993, 1995a,b; Swan et al., 1998a; Waldstein et al., 1991). In point, separate cross-sectional MRI studies indicate that compared with their normotensive counterparts, individuals with self-reported or medically treated hypertension show lower volumes of the left hemisphere (Salerno et al., 1992), the entire prefrontal cortex (defined inclusively as Brodmann areas 8, 9, 10, 11, 45, 46, and 47; Raz et al., 2003), the bilateral thalamus (Strassburger et al., 1997), and the bilateral hippocampal complex (Wiseman et al., 2004). Findings from prospective MRI studies – in which blood pressure was measured several years prior to when brain tissue volume was estimated – are also dissimilar. Such prospective studies, for example, have separately reported that higher midlife blood pressure predicts a lower volume of total brain tissue (DeCarli et al., 1999), a lower volume of total cortical tissue (den Heijer et al., 2003), and a lower volume of the bilateral hippocampus (Korf et al., 2004) later in life. A precise summary of the disparate findings from these prior studies of blood pressure and brain tissue volume is difficult, however, because these studies differ in their methodology.

First, prior studies differ in how they defined an individual's blood pressure status, with many studies using self-reports of prior treatment for hypertension, nonstandard statistical criteria (e.g., upper vs. lower quartile), or varying clinical cutoffs to define blood pressure groups. Second, few studies have used the same method to quantify the volume of the same brain region or the same type of brain tissue (e.g., grey, white, or total brain matter). And third, studies differ as to whether they have accounted for such factors as age, sex, treatment for hypertension, and comorbid medical conditions that may modify and confound the relationships between blood pressure, regional brain tissue volume, and cognitive function.

In light of these methodological factors, we first asked whether a higher resting systolic or diastolic blood pressure predicts a lower grey or white matter tissue volume in specific brain regions. To answer this question, we used optimized voxel-based morphometry, a semi-automated and validated method to derive quantitative estimates of grey and white matter volume on a voxel-wise basis (Ashburner and Friston, 2000; Good et al., 2001b, 2002). We also asked whether a blood-pressure-related reduction in regional grey or white matter volume has measurable consequences on cognitive function. To answer this second question, we first extracted the regional brain tissue volumes from those areas in which a higher blood pressure predicted a lower volume. We then used these volume estimates as predictors of performance on neuropsychological tests of executive control, working memory, and general intellectual ability after controlling statistically for age, number of years of education, resting blood pressure, severity of carotid atherosclerosis (as indicated by carotid intima-media thickness), and the extent of ischemic small-vessel white matter neuropathology (as indicated by the grade of white matter hyperintensities). Participants were otherwise healthy adults who were not treated for hypertension at the time of the study, in the 1-year period prior to the study, or for any period of 12 months or more at any time in their lives.

Methods

Participants

Participants were 134 adults (76 men, 58 women) aged 50–70 years who were recruited by mass mailings and media advertisements in Allegheny County, PA, USA. Exclusion criteria were secondary hypertension; current use of anti-hypertensive, cardiovascular-active, or psychotropic medication; lifetime treatment for hypertension exceeding 12 months; any treatment for hypertension in the 12 months preceding study entry; a prior stroke, myocardial infarction, or traumatic head injury; prior vascular surgery; congestive heart failure or pulmonary disease; diabetes; obesity (>30% overweight by Metropolitan Life Insurance tables); cancer; renal failure (determined by serum creatinine >2.0 mg/dl); hepatitis; cirrhosis; a substance abuse or alcohol disorder; consumption of more than 15 alcoholic beverages per week; a psychiatric disorder; and reading skills below an eighth-grade level. Fourteen men and 9 women reported being current smokers; 70 men and 56 women reported being right-handed. All women tested were postmenopausal and were not receiving hormone replacement therapy. All participants provided informed consent, and the University of Pittsburgh's Institutional Review Board granted study approval.

Study protocol

Participants completed five testing sessions that included (1) a medical screening session to establish study eligibility, obtain demographic information and a health history, and measure resting blood pressure; (2) a neuropsychological testing session to determine performance on tests of executive control, memory, and general intellectual ability; (3) an ultrasound scanning session to determine the severity of carotid atherosclerosis; (4) a structural MRI session to assess brain tissue volume and the grade of white matter hyperintensities; and (5) a positron emission tomography scanning session to determine regional cerebral blood flow responses to working memory tasks (the protocol and results for session 5 are reported in Jennings et al., 2005). The five testing sessions were completed on different days over a median time period of 2 weeks.

Assessment of resting blood pressure

At the first testing session, three auscultatory measures (separated by approximately 2 min) of resting blood pressure were obtained from the brachial artery of each participant's nondominant arm. Blood pressure was measured while the participant was seated and after she or he rested in that position for 10 min (Kirkendall et al., 1980). Diastolic pressure was taken as the pressure at which the last Korotkoff sound was heard (Phase IV). The same method was used to measure blood pressure at the beginning of the second (neuropsychological) testing session. After discarding the first measurement, we averaged the final two blood pressure measurements across both sessions and used the average of these four measures as an estimate of resting blood pressure. Thirty-eight percent of the men (29/76) and 22% of the women (13/58) in the present sample had blood pressures in the hypertensive range, defined as a systolic blood pressure exceeding 140 mm Hg, a diastolic blood pressure exceeding 90 mm Hg, or both.

Assessment of neuropsychological test performance

In the second testing session, we assessed executive control and working memory processes with a battery of neuropsychological tests. From the battery (described fully in Jennings et al., 2005), we selected performance scores on the Trail Making Test (TMT) Parts A and B (Reitan, 1958; Spreen and Strauss, 1998) and the Four-word Short-term Memory Test (FWSTM; Morrow and Ryan, 2002). We also evaluated performance on a test of general intellectual ability, the National Adult Reading Test (Nelson, 1991). The selection of performance on the TMT and FWSTM was guided by the hypothesis that executive control and working memory,

the two cognitive functions assessed by these tests, are mildly impaired in part by the adverse effects of high blood pressure on brain tissue volume (e.g., Moore et al., 2002; Raz et al., 2003).

The TMT Part B requires the participant to alternately connect numbered and lettered circles as quickly and as accurately as possible (i.e., $1 > A > 2 > B > 3$, etc.). Faster completion times (in seconds) indicate greater executive control or a better flexibility to shift attention between changing stimulus sets and to execute planned motor responses. TMT Part B performance, however, may be influenced by individual differences in psychomotor speed, which is assessed by the time to connect consecutively numbered circles in the TMT Part A (Lezak, 1995; Schear and Sato, 1989; Steinberg et al., 2005; Stuss et al., 1987; Waldstein et al., 1991). To control for psychomotor speed, we regressed completion times for the TMT Part B on completion times for the TMT Part A ($r_{\text{TMT B} \cdot \text{A}} = 0.49$, $P < 0.001$), and we retained the resulting standardized residual (observed minus predicted) values. Standardized residual TMT Part B values were used in all correlation and regression analyses.

The FWSTM is a test of working memory that is based on the Brown–Peterson paradigm (Brown, 1958; Peterson and Peterson, 1959). The FWSTM requires the participant to remember a list of four unrelated words, which are read aloud to the participant at a rate of one word per second. After the list is read, the participant is instructed to count backwards aloud as rapidly and as accurately as possible by 3 s from a three-digit seed number for 5-, 15-, and 30-s intervals. At the end of each interval, the participant is asked to recall the words from the list. The distracting counting task is intended to prevent the participant from rehearsing the to-be-recalled list. Recall for different four-item lists was assessed five times for each of the three intervals (5, 15, and 30 s), yielding a maximum possible score of 20 correctly recalled items for each interval. Because exploratory data analyses showed that the distributions of correctly recalled items at each interval were skewed, they were corrected with a natural log transformation prior to statistical analyses; they are shown for descriptive purposes in raw form in Table 1 and Fig. 4.

Table 1 shows that the number of items correctly recalled for the FWSTM and that the completion times for the TMT Parts A and B are comparable to population-based normative values for these tests (Morrow and Ryan, 2002; Steinberg et al., 2005; Stuss et al., 1987). As shown in Table 1, women had a slight performance advantage for both tests, which reached statistical significance for the TMT Part A and for each recall interval of the FWSTM. Although men completed approximately 1 additional year of schooling compared with women, men and women did not differ in their general intellectual ability, as assessed by the NART (see Table 1); nor did they differ in their standardized TMT Part B scores that were adjusted for TMT Part A scores (mean difference = 0.07 standardized units; 95% confidence interval of the difference = -0.28 to 0.43).

Assessment of carotid artery atherosclerosis

In the third testing session, we assessed mean carotid intima-media thickness (IMT), an indicator of preclinical (symptom-free) carotid atherosclerosis. Greater carotid IMT correlates strongly with higher blood pressure, and it is a risk factor for clinical cardiovascular and cerebrovascular disease (Bots et al., 1997; Heiss et al., 1991; Hodis et al., 1998; Lakka et al., 1999; O'Leary and Polak, 2002; van der Meer et al., 2003). We determined mean carotid IMT using B-Mode ultrasonography. To derive mean IMT, a trained sonographer scanned the right and left common external carotid arteries, carotid bifurcation, and first centimeter of the internal carotid artery with a Toshiba SSA-270 scanner, which was equipped with a 5-MHz linear-array ultrasound probe. The mean distance (in mm) was calculated between lumen-intima and media-adventitia interface across the three carotid segments: (1) the near and far walls of the right and left common carotid arteries (1 cm proximal to the carotid bulb); (2) the

far wall of the carotid bulb (starting at the point at which the near and far walls are no longer parallel and ending at the flow divider); and (3) the far wall of the internal carotid artery (from the flow divider to the first centimeter distal to this point). The data in Table 1 show that mean carotid IMT for men and women in the present sample was comparable to age- and sex-matched distributions from other adult community samples (Heiss et al., 1991; O'Leary and Polak, 2002; van der Meer et al., 2003), with men showing an average of .07 mm greater IMT than women (95% confidence interval of the difference = 0.009 to 0.115 mm).

Assessment of magnetic resonance imaging indicators of brain tissue volume and white matter hyperintensities

At the fourth testing session, we obtained structural magnetic resonance images with a 1.5-T Signa scanner (GE Medical Systems, Milwaukee, WI) and a standard birdcage radiofrequency head coil. Coronal images for the assessment of brain tissue volume were acquired with a T_1 -weighted 3D spoiled gradient recalled (SPGR) acquisition sequence (TE = 5 ms; TR = 25 ms; flip angle = 40°; NEX = 1), which provided 124 slices (1.5 mm thick; 0 mm spacing between slices; matrix size = 256 × 192 pixels; FOV = 24 × 18 cm). After acquisition, SPGR images were re-sampled to contain 1 mm³ isotropic voxels that were axially reoriented and aligned to the plane of the anterior and posterior commissures.

Axial images that were used to grade the extent of white matter hyperintensities and to inspect for signs of prior cerebral infarctions were obtained with a fast fluid-attenuated inversion recovery (FLAIR) sequence (effective TE = 56 ms; TR = 9002 ms; TI = 2200 ms; NEX = 1), a fast spin echo T_2 -weighted sequence (effective TE = 102 ms; TR = 2500 ms; NEX = 1), and a proton density-weighted sequence (effective TE = 17 ms; TR = 2000 ms; NEX = 1). All axial pulse acquisition sequences were oriented to the plane of the anterior and posterior commissures (5 mm slice thickness; 1 mm spacing between slices; matrix size = 256 × 192 pixels; FOV = 24 cm).

The extent of white matter hyperintensities was determined qualitatively by two trained readers who graded the FLAIR images for the total volume of white matter signal hyperintensities in both periventricular and subcortical areas (Jennings et al., 2005). White matter hyperintensity grades (averaged across periventricular and subcortical regions) were assigned to each image using the standardized 9-point scale of the Cardiovascular Health Study, which is anchored by 0 = absent and 8 = extensive (Bryan et al., 1994; Longstreth et al., 1996; Manolio et al., 1994). One participant who showed signs of a prior infarction (determined by a neuroradiologist who inspected all MR images) was excluded from further study. Table 1 shows that men and women in the present sample had comparably minimal white matter grades.

Optimized voxel-based morphometry assessment of regional grey and white matter volume

To determine regional (voxel-wise) grey and white matter volumes, we used optimized voxel-based morphometry (Ashburner and Friston, 2000; Good et al., 2001a,b). All voxel-based morphometry processing steps were performed using statistical parametric mapping software (SPM2; Wellcome Trust Centre for the Study of Cognitive Neurology; <http://www.fil.ion.ucl.ac.uk/spm/spm2.html>), which was implemented in Matlab version 6.5.1 on an Apple Macintosh platform.

In the first processing step, grey matter, white matter, and cerebrospinal fluids were segmented with a mixture model cluster analysis that was applied to each participant's T_1 -weighted SPGR image. To segment grey matter, white matter, and cerebrospinal fluid, the mixture model used customized Bayesian prior probability maps (templates) of the three tissue types. Customized templates were created from SPGR images that were obtained from a separate sample of 330 healthy older men and women (mean age = 67 ± 7.5 years) who were scanned in the same 1.5-

T scanner and with the same SPGR acquisition sequence as were participants in the present study. These customized templates were registered to the anatomical space of the Montreal Neurological Institute, and they were used to better represent the Bayesian prior tissue probabilities and the brain morphology of the present study's older sample. All individuals who contributed images to the customized templates were determined to be free of signs of cerebrovascular pathology by a consensus panel of neuroradiologists (for details about the template construction, see Spears et al., 2005). The templates are available from the corresponding author, and sections of the grey matter template are illustrated in Fig. 1 and Fig. 2.

In the second processing step, segmented images were spatially normalized to the anatomical space of the Montreal Neurological Institute. Spatial normalization was achieved with affine transformations and linear combinations of smooth basis functions that minimized global (and nonlinear) squared differences between individual segmented images and their corresponding tissue-specific template. In the third processing step, the parameters that were generated from spatial normalization were then re-applied to the original, nonsegmented structural images (in their native space) to facilitate optimal tissue segmentation. This third step minimizes the contribution of nonbrain voxels and tissue misclassification (partial voluming) to the final voxel-wise volume estimates (Good et al., 2001b). In the fourth step, spatially normalized images were then re-segmented into grey matter, white matter, and cerebrospinal fluid with our customized elderly templates as Bayesian prior tissue probability maps. In the final step, optimally segmented and spatially normalized images were multiplied (modulated) by the Jacobian matrix determinants that were derived from spatial normalization. This final modulation step incorporates into each voxel value the volume change that was applied to that voxel during nonlinear spatial normalization. These modulated images provided voxel-wise volume values in milliliters. The data in Table 1 show that men had greater total volumes of grey and white matter than women.

Prior to statistical analyses, modulated grey and white matter tissue volume images were smoothed in the x , y , and z dimensions with a 12-mm FWHM isotropic Gaussian kernel to accommodate between-participant differences in brain morphology and to meet the distribution assumptions of the general linear models that were used to examine the relationships between blood pressure and regional (voxel-wise) grey and white matter volume (Friston et al., 1995; Salmond et al., 2002).

Data analysis

Blood pressure and regional brain tissue volume—We first asked whether higher resting systolic or diastolic blood pressures (both treated as continuous variables) predicted lower grey or white matter volume on a voxel-wise basis after controlling for age and total brain tissue volume. To answer this question, we conducted four separate analyses in SPM2 using the framework of the general linear model (Friston et al., 1995). One model tested for the relationship between systolic blood pressure and grey matter volume, one for diastolic blood pressure and grey matter volume, one for systolic blood pressure and white matter volume, and one for diastolic blood pressure and white matter volume. Systolic and diastolic blood pressures were tested in separate models because of their high correlation ($r = 0.62$, $P < 0.001$), which caused a multicollinearity problem in exploratory analyses. In all four models, age, sex, and resting blood pressure were treated as explanatory factors, and total brain tissue volume (the sum of total grey and white matter volumes) was treated as a nuisance factor (covariate of no interest). In all models, we included sex-by-blood pressure, age-by-blood pressure, and sex-by-age-by-blood pressure interaction terms—after mean centering the explanatory factors in the model. The false discovery rate procedure was used to correct voxel-wise P values for conducting multiple statistical tests (Genovese et al., 2002).

Brain tissue volume and neuropsychological test performance—After testing whether higher blood pressure predicted lower regional grey or white matter volume, we next tested whether a blood-pressure-related reduction of brain tissue volume predicted slower TMT Part B completion times (adjusted for TMT Part A completion times), poorer recall on the FWSTM, or lower scores on the NART. For these analyses, we extracted tissue volume values from all voxels in a 6-mm radius (1/2 of our Gaussian smoothing kernel) surrounding the voxel of peak correlation between blood pressure and brain tissue volume. We then used these aggregate volume values as predictors of neuropsychological test performance in two-step hierarchical linear regression analyses (Cohen and Cohen, 1983). In step 1, we entered as covariates all potentially confounding variables that correlated at $P < 0.20$ with performance on any of the neuropsychological tests in exploratory univariate correlation analyses. Using this approach, step 1 covariates for all hierarchical models included age, years of education, resting blood pressure, mean carotid IMT, and white matter grade. In step 2, we entered the volume value for the brain region in which higher blood pressure predicted lower tissue volume. The unique percentage of variance in neuropsychological test performance explained by the regional volume value in step 2 was evaluated by the ΔR^2 in the second step of the model.

Results

Grey matter

Systolic blood pressure—Among men, a higher resting systolic blood pressure predicted a lower grey matter volume in four brain regions: Brodmann area 6 of the supplementary motor area, adjacent area 8 of the superior frontal gyrus, area 24 of the right anterior cingulate cortex, and area 21 of the left middle temporal gyrus. Among women, systolic blood pressure did not predict regional grey matter volume at corrected or at uncorrected levels of voxel-wise statistical significance. These results were revealed by sex-by-systolic blood pressure interactions in a general linear model that predicted voxel-wise grey matter volume while treating age as an additional explanatory factor and total brain tissue volume as a nuisance variable (see Table 2; Fig. 1 and Fig. 2). Panels A–D of Fig. 3 illustrate the strength of the association between systolic blood pressure and regional grey matter volume among men and women. Among men, systolic blood pressure accounted for a moderate percentage of the variance in the grey matter volume of Brodmann areas 6, 8, 24, and 21 (R^2 ranges 0.07 to 0.14, P s < 0.05). By contrast, among women, systolic blood pressure did not account for a statistically significant proportion of the variance in the grey matter volume of any of these four regions (R^2 ranges 0.001 to 0.04, P s, ns).

In separate univariate correlation analyses, we also evaluated the relationships between resting systolic blood pressure and *total* grey and white matter volumes. We found that when men and women were considered together, resting systolic blood pressure did not account for a statistically significant proportion of the variance in total grey matter volume ($r = -0.06$, $P = 0.49$). Similar results were obtained when men ($r = -0.16$, $P = 0.19$) and women ($r = -0.09$, $P = 0.47$) were considered separately.

Diastolic blood pressure—Resting diastolic blood pressure did not predict regional grey matter volume among the entire sample or among men and women considered separately. These null results were verified both at corrected and at uncorrected voxel-wise statistical significance thresholds. In addition, diastolic blood pressure did not account for a statistically significant proportion of the variance in *total* grey matter volume among the entire sample or among men and women considered separately (all r s < 0.10 , P s > 0.60).

Age—As expected, higher age predicted a lower grey matter volume in several brain regions, most notably in bilateral thalamic regions surrounding the ventricles and in frontal, temporal,

and insular regions of the cortex (see Table 3; Fig. 1 and Fig. 2). Of note, the brain regions where grey matter volume decreased as a function of higher age were spatially distinct from those regions where grey matter volume decreased as a function of higher systolic blood pressure among men (see Fig. 1 and Fig. 2). In addition, none of the voxel-wise higher order (three-way) interaction terms between age, sex, and systolic blood pressure reached corrected or uncorrected voxel-wise statistical significance thresholds.

Post hoc general linear models also showed that other potentially confounding factors (smoking status, years of education, carotid IMT, and white matter grade) did not predict regional grey matter volume. Adding these factors to the general linear models described above also did not change the pattern or the statistical significance of the results that are illustrated in Fig. 1–Fig. 3 and that are summarized Tables 2 Tables 3 (null results omitted).

White matter

Among the entire sample and among men and women considered separately, neither systolic nor diastolic blood pressure predicted regional white matter volume at corrected or uncorrected voxel-wise statistical significance thresholds nor did systolic and diastolic blood pressure predict *total* white matter volume (all $r_s < 0.10$, $P_s > 0.40$).

Grey matter volume and neuropsychological test performance

Having established that a higher resting systolic blood pressure among men predicted a lower grey matter volume in Brodmann areas 6, 8, 24, and 21, we next tested whether lower grey matter volumes in these four regions predicted poorer performance on the TMT Part B, the FWSTM, or the NART. Because men and women differed in the relationship between systolic blood pressure and grey matter volume in these four regions, we examined the data for men and women separately (see Table 4 for a summary of sex-specific univariate correlations between grey matter volume and test performance).

Men—Among men, only lower grey matter volume in Brodmann area 6 of the supplementary motor area independently predicted slower times to complete the TMT Part B and poorer recall at the 5-s (but not the 15- or 30-s) interval on the FWSTM. These results were revealed by two-step hierarchical regression analyses that predicted performance on the TMT Part B (adjusted for TMT Part A) and recall on the FWSTM from grey matter volume in area 6. In these analyses, the following confounders were entered as covariates in step 1: age, educational history, systolic blood pressure, carotid IMT, and white matter grade (see Table 5 and Table 6; Fig. 4). As shown in Table 5 and Table 6, grey matter volume in area 6 among men accounted for 6% of the unique variance in TMT Part B performance and 5% of the unique variance in FWSTM performance at the 5-s distracter interval—above and beyond the variance accounted for by all covariates. In contrast, grey matter volume in area 6 did not account for a significant proportion of the variance in overall intellectual ability, as indicated by NART performance (step 2 $\Delta R^2 = 0.02$, $F = 2.78$, $P = 0.17$).

Corroborating the univariate correlations shown in Table 4, two-step hierarchical regression analyses showed that the grey matter volumes of areas 8, 24, and 21 among men did not predict performance on the TMT Part B, the FWSTM, or the NART after statistical control for the same covariates listed in Table 5 and Table 6 (null results omitted).

Women—Among women, there were no statistically significant relationships between performance on the TMT Part B, FWSTM or on the NART and grey matter volumes in areas 6, 8, 24, and 21 (see Table 4).

Discussion

The first main finding of the present study is that a higher resting systolic blood pressure among men, but not women, predicts lower grey matter volume in four specific cortical regions: Brodmann area 6 of the supplementary motor area, adjacent area 8 of the superior frontal gyrus, area 24 of the anterior cingulate cortex, and area 21 of the left temporal lobe. The second main finding is that among men, a lower grey matter volume in area 6 predicts poorer performance on two neuropsychological tests of short-term information processing, but not on a test of general intellectual ability. Both of these findings held after statistical control for several potential confounders, including age, total brain tissue volume, educational history, severity of carotid atherosclerosis, and extent of periventricular and subcortical white matter lesions. As such, the present study provides evidence for a functional relationship between higher systolic blood pressure, lower regional grey matter volume, and poorer cognitive function that may be specific to middle-aged men.

Our main findings build on two prior studies of regional brain tissue volume and cognitive function among individuals with hypertension. In the first study, Salerno et al. (1992) reported that 18 men with long-standing (10- to 35-year duration) and treated hypertension showed larger lateral ventricles (indicating diffuse subcortical atrophy) and a lower volume of the left hemisphere than 17 age-matched men without hypertension. However, in region-of-interest analyses confined to the thalamus and basal ganglia, Salerno et al. found no differences in regional brain tissue volume between men with and without hypertension. In addition, estimates of ventricular size, hemispheric volume, and volumes of the thalamus and basal ganglia did not predict neuropsychological test performance. Salerno et al., however, did not test for relationships between volume estimates from cortical brain regions and cognitive function—as was done in the present study and in another study of individuals with treated hypertension (Raz et al., 2003). In that study, Raz et al. found that compared with a control sample, individuals with self-reported and treated hypertension showed a lower total volume of the prefrontal cortex (defined inclusively as Brodmann areas 8, 9, 10, 11, 45, 46, and 47) and committed more preservative errors on the Wisconsin Card Sorting Task, which indicates impaired executive control.

The present findings complement and extend these prior findings to an untreated sample by showing a continuous relationship among men between higher systolic blood pressure and lower grey matter volume in four regions of the frontal (Brodmann areas 6, 8, and 24) and temporal (Brodmann area 21) cortices. Also extending prior work, the present study indicates that there is a possible functional consequence of a blood-pressure-related reduction in the grey matter volume of the supplementary motor area. More precisely, among men, a lower grey matter volume in the supplementary motor area independently predicted poorer performances on two tests of short-term information processing, the TMT Part B and the FWSTM.

Lying along the superior and medial surface of the premotor cortex, the supplementary motor area receives afferent projections from posterior parietal regions (areas 5 and 7) and primary somatosensory regions (areas 3, 1, 2). The supplementary motor area also sends efferent projections to the basal ganglia and cerebellum, which, along with the primary motor cortex, execute and correct planned behaviors (Alexander and Crutcher, 1990; Hoover and Strick, 1993). There is both lesion and functional imaging evidence that the supplementary motor area supports short-term information processing and executive functions, such as behavioral planning (Gentilucci et al., 1997; Rushworth et al., 2004). And, germane to the present findings, there is recent functional neuroimaging evidence that area 6 of the supplementary motor area is engaged by a modified version of the TMT Part B (Moll et al., 2002).

In the present study, a lower grey matter volume in area 6 of the supplementary motor area among men predicted a slower time to complete the TMT Part B, which may reflect a subtle disruption in the execution of planned motor responses that are coordinated with attention to a changing stimulus set. A lower grey matter volume in area 6 among men also predicted poorer recall at the 5-s distracter interval of the FWSTM, but not the longer 15- and 30-s intervals, which may reflect a subtle disruption in the capacity of shorter-term working memory under dual-task conditions. In the present sample, performance on the TMT Part B and recall at the 5-s interval were moderately correlated ($r = -0.23$, $P < 0.05$), which suggests some overlap in the short-term information processing functions that are assessed by these two tests.

In comparison to the findings for the TMT Part B and the FWSTM, grey matter volume in area 6 among men did not predict general intellectual ability, as indicated by scores in the National Adult Reading Test. In addition, the grey matter volume of the three other cortical regions (areas 8, 24, and 21) where grey matter decreased as a function of increasing systolic blood pressure among men did not predict neuropsychological test performance apart from other confounding factors. Given this set of findings, we speculate that among middle-aged men, a blood-pressure-related reduction in regional grey matter volume – specifically in Brodmann area 6 – may disrupt efficient short-term information processing but not general intellectual ability.

This speculation is consistent with the hypothesis that executive functions, such as those that are assessed by the TMT Part B and the FWSTM, may be subtly disrupted by the ischemic effects of high blood pressure on frontal lobe regions that are supplied by the middle and anterior cerebral arteries (DeCarli et al., 1995, 2001; Kemper et al., 2001; Kramer et al., 2004; Raz et al., 2003, 2005; Swan et al., 1998b; Waldstein et al., 1991). Further, in support of this speculation, there is evidence from primate and rodent models that chronic high blood pressure may contribute to cerebral ischemia, to hypoperfusion of brain tissue, and to breaches in the integrity of the blood–brain and blood–cerebral spinal fluid barriers—all of which may promote neuropathology and atrophy in vulnerable frontal regions (Al-Sarraf and Philip, 2003a,b; Kemper et al., 2001; Moore et al., 2002; Tajima et al., 1993).

In conjunction with chronic cerebral ischemia, high blood pressure may also contribute to acute cerebral ischemia that may restrict ongoing regional cerebral blood flow to brain regions that support working memory and executive functions. For example, functional neuroimaging studies demonstrate that individuals with hypertension show both decreased and compensatory patterns of regional cerebral blood flow during the performance of tasks that engage working memory and executive control processes (Jennings et al., 1998, 2005; Salerno et al., 1995). Taken together with the present findings, there is thus accumulating support for the hypothesis that high blood pressure may impair specific cognitive functions through both chronic and acute ischemic effects on regional brain structure and function.

The relationship between higher systolic blood pressure, lower regional grey matter volume, and poorer neuropsychological test performance was specific to men. As has been found in prior studies, men and women differed in their total grey and white matter tissue volumes. Importantly, these sex differences did not explain our results: total brain tissue volume was treated as a covariate in all general linear models. Further, men and women did not differ in age, a factor that could also affect brain tissue volume. One explanation of our findings is that men in the present study were exposed to the chronic cerebral ischemic effects of higher blood pressure for a longer period of time than were women—thus promoting greater blood-pressure-related reductions in regional grey matter volume. Blood pressure and other cerebrovascular risk factors rise with age approximately 10 years earlier in men than in women (Anastos et al., 1995; Kaplan, 1995; Lerner and Kannel, 1986; Messerli et al., 1987; Pickering, 1955; Safar and Smulyan, 2003). Therefore, if higher blood pressure and other risk factors develop later

during aging in women than in men, then women may show an inverse relationship between systolic blood pressure and regional grey matter volume later in life—as they are exposed to a longer duration of high blood pressure. Consistent with this speculation, a longer duration of high blood pressure was associated with a greater ventricular dilation in the report by Salerno et al. (1992) and a lower prefrontal cortical volume in the study by Raz et al. (2003). However, without prior measures of blood pressure or follow-up assessments of regional brain tissue volume, the present cross-sectional study cannot resolve whether the length of exposure to high blood pressure or other risk factors contributes to sex-by-blood pressure interactions in the prediction of grey matter volume.

Higher blood pressure did not correlate with regional white matter tissue volume in the present study. To our knowledge, no prior studies have investigated the relationships between blood pressure and voxel-wise white matter volume. There is longstanding evidence that higher blood pressure is associated with a greater severity of ischemic small-vessel neuropathology, as indicated by a greater burden of white matter hyperintensities (Dufouil et al., 2001; Longstreth et al., 1996; Skoog, 1998). As speculated previously, a greater burden of white matter hyperintensities may contribute to cognitive impairments in hypertension (Decarli, 2004; DeCarli et al., 1995, 1999, 2001; Dufouil et al., 2001; Gunning-Dixon and Raz, 2000; Reinhold et al., 1995; Salerno et al., 1992; Sierra et al., 2004; Skoog, 1998; Swan et al., 1998b). However, after statistical control for white matter grade, a higher systolic blood pressure continued to predict a lower regional grey matter volume among men. Similarly, after statistical control for white matter grade, a lower grey matter volume in area 6 continued to predict poorer performance on the TMT Part B and the FWSTM. These findings indicate that the relationships between higher systolic blood pressure, lower regional brain tissue volume, and poorer short-term information processing among men were specific to grey matter brain tissue, and that they were independent of white matter burden.

Higher systolic blood pressure correlates with higher age, which itself correlates with MRI indicators of brain atrophy and cognitive decline (Good et al., 2001b; Kramer et al., 2004; Raz et al., 2005). Consistent with prior studies, we found that higher age predicted a lower grey matter volume in somatosensory, parietal, orbitofrontal, and hippocampal brain regions (Lemaitre et al., 2005; Raz et al., 2005); however, a higher systolic blood pressure predicted a lower grey matter volume in brain regions that were spatially distinct from those in which higher age predicted lower grey matter volume among men (see Fig. 1 and Fig 2). In all, these results suggest that higher blood pressure may adversely affect brain regions other than those that show typical age-related declines in grey matter volume.

The present study was conducted on a relatively well-educated and healthy sample of middle-aged men and women. Therefore, our sample may not be representative of the general population. With the exception of the 42 individuals who had untreated hypertension, none of our participants had a psychiatric, neurological, cerebrovascular, or cardiovascular disease. Higher blood pressure is prevalent among individuals with such secondary medical conditions, and it correlates with other risk factors that may also affect brain structure and cognition. Thus, it is possible that the present findings in otherwise healthy individuals may underestimate the strength of the relationships between higher blood pressure, regional brain tissue volume, and cognitive function that characterize the general population. In addition, because the present study was cross-sectional, we cannot exclude the possibility that a lower regional grey matter volume contributes to a higher resting blood pressure among men. Arguing against this possibility, however, are (1) prior longitudinal studies that show that higher midlife blood pressures precede a reduction in brain tissue volume (DeCarli et al., 1999; den Heijer et al., 2003; Korf et al., 2004; Swan et al., 1998b) and (2) prior animal studies that show that chronic high blood induces cerebral ischemia and consequent neuropathology (Al-Sarraf and Philip, 2003a,b; Gesztelyi et al., 1993; Kemper et al., 2001; Tajima et al., 1993).

To conclude, there is emerging evidence that high blood pressure is a plausible risk factor for diffuse brain atrophy. However, high blood pressure has not been consistently associated with a focal reduction in regional brain tissue volume. This voxel-based morphometry study provides evidence that higher resting systolic blood pressure among men, but not women, predicts lower grey matter volumes in the supplementary motor area, superior frontal gyrus, anterior cingulate cortex, and middle temporal lobe. Moreover, after adjusting for several potential confounders, lower grey matter volume in the supplementary motor area predicted poorer performance on tests of executive control and working memory — cognitive functions that are often subtly impaired among individuals with hypertension. Such relationships between higher blood pressure, lower regional grey matter volume, and poorer cognitive have not yet been characterized to our knowledge in a sample of untreated and otherwise healthy men and women. In line with prior animal and human MRI studies, we speculate that higher blood pressure may be a risk factor for focal brain atrophy, but that the effects of higher blood pressure on brain tissue volume may be modified by sex differences in the development and duration of chronic high blood pressure. A new question with clinical implications is whether exercise, diet, or pharmacological interventions that lower blood pressure and improve cognitive function also protect against blood-pressure-related reductions in grey matter.

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Abbreviations

FOV, field of view; FWHM, full width at half maximum; NEX, number of excitations; TE, time to echo; TI, time to inversion; TR, time to repetition..

Fig. 1.

Profiled in color are brain regions in which higher age (blue–green) and a sex-by-systolic blood pressure interaction (red–yellow) predicted a lower grey matter volume. The sex-by-blood pressure interaction was explained by men ($n = 76$), but not women ($n = 53$), showing a lower regional grey matter volume as a function of higher systolic blood pressure (see Fig. 3). Color-scaled t values (legends at lower right) were derived from a general linear model of voxel-wise grey matter volume that included total brain tissue volume as a nuisance variable. Montreal Neurological Institute coordinate values below each section of a grey matter template refer to the distance in millimeters relative to the midline for sagittal sections in this figure (+ = right; – = left) and to the anterior commissure for coronal sections in Fig. 2 (+ = anterior; – = posterior). In each section, white matter and cerebrospinal fluid are blackened.

Fig. 2.

Profiled in color are brain regions in which higher age (blue–green) and a sex-by-systolic blood pressure interaction (red–yellow) predicted a lower grey matter volume. The sex-by-blood pressure interaction was explained by men ($n = 76$), but not women ($n = 53$), showing a lower regional grey matter volume as a function of higher systolic blood pressure (see Fig. 3). Color-scaled t values (legends at lower right) were derived from a general linear model of voxel-wise grey matter volume that included total brain tissue volume as a nuisance variable. Montreal Neurological Institute coordinate values below each section of a grey matter template refer to the distance in millimeters relative to the midline for sagittal sections in Fig. 1 (+ = right; – = left) and to the anterior commissure for coronal sections in this figure (+ = anterior; – = posterior). In each section, white matter and cerebrospinal fluid are blackened.

Fig. 3.

Higher resting systolic blood pressure among men ($n = 76$), but not women ($n = 58$), predicted lower grey matter volumes in Brodmann areas 6, 8, 24, and 21. Grey matter volumes (shown along the y-axes) represent the sum of all volume values from those voxels within a 6 mm radius of the x , y , and z coordinates for the region in which sex and systolic blood pressure interacted to predict grey matter volume (see Table 2 for the coordinates for each region of interaction). Correlation coefficients off of each dotted line are for men (closed circles, solid lines) and women (open circles, dashed lines).

Fig. 4.

Lower grey matter volume in Brodmann area 6 of the supplementary motor area was associated with higher resting systolic pressure and poorer performance on the Trail Making Test Part B (panel A) and the Four-word Short-term Memory Test (panel B) among 76 men. Shown along the x -axis of both panels are grey matter volume values for all voxels in a 6 mm radius surrounding the region of the supplementary motor area where higher systolic blood pressure predicted lower grey matter volume (Montreal Neurological Institute coordinates are $x = -6$, $y = 23$, $z = 55$). Shown along the y -axis in panel A are standardized Trail Making Test Part B completion times, adjusted for Trail Making Test Part A completion times (see Methods). Lower standardized Trail Making Test Part B completion times indicate better performance. Shown along the y -axis in panel B is the number of correctly recalled items after a 5-s distracting interval from the Four-word Short-term Memory Test.

Table 1

Sample characteristics of 76 men and 58 women

Variable	Men		Women		All individuals mean (SD)
	Mean (SD)	Range	Mean (SD)	Range	
Age (years)	61.3 (5.0)	50–70	59.9 (5.1)	52–70	60.7 (5.0)
Education (years)	15.6 (2.9)	11–23	14.2 (2.3) *	11–21	15.0 (2.7)
Mean carotid IMT (mm)	0.87 (0.17)	0.61–1.49	0.80 (0.12) *	0.59–1.27	0.83 (0.16)
White matter grade ^a	1.34 (0.98)	0–4.5	1.29 (0.99)	0–4.0	1.32 (0.98)
Blood Pressure					
SBP (mm Hg)	132.4 (15.5)	105.0–171.5	128.8 (15.0)	93.5–172.0	130.8 (15.3)
DBP (mm Hg)	79.3 (8.0)	62.0–98.0	76.58 (9.3)	57.5–95.5	78.1 (8.7)
Neuropsychological test performance					
Trail Making Part A (s)	31.5 (10.9)	16.0–76.0	27.7 (9.6) *	12.0–56.0	30.1 (10.5)
Trail Making Part B (s)	79.6 (32.9)	35.0–216.0	71.79 (30.5)	31.0–171.0	76.5 (32.0)
FWSTM (items recalled)					
5 s	14.6 (2.7)	8–20	16.2 (2.2) *	11–20	15.2 (2.6)
15 s	10.8 (3.4)	4–19	12.6 (3.2) *	4–19	11.5 (3.4)
30 s	8.7 (3.7)	1–17	10.7 (3.7) *	4–19	9.5 (3.8)
NART score	108.6 (11.3)	77.9–127.8	109.8 (7.4)	91.3–122.5	109.1 (9.8)
Brain tissue volume (ml)					
Total grey matter	653.3 (48.1)	504.9–773.1	602.2 (49.9) *	465.2–733.5	631.2 (54.9)
Total white matter	439.3 (41.5)	344.0–545.0	386.2 (35.1) *	325.1–503.7	416.3 (46.8)
Total grey + white	1092.5 (82.6)	848.9–1313.9	988.4 (76.1) *	790.3–1237.2	1047.5 (94.9)

Note. IMT = intima-media thickness; SBP = systolic blood pressure; DBP = diastolic blood pressure; FWSTM = Four-word Short-term Memory Test; NART = National Adult Reading Test.

^aWhite matter grade was coded on a 0–8 point scale (see Methods section).

* Sex difference of $P < 0.05$ (two tailed).

Brain areas where sex and systolic blood pressure interacted to predict lower grey matter volume in 76 men and 58 women

Table 2

Side	Region	BA	MNI coordinates			t value	pFDR
			x	y	z		
L	Supplementary motor area	6	-6	23	55	4.65	.03
L	Superior frontal gyrus	8	-26	21	41	4.37	.03
R	Anterior cingulate cortex	24	1	10	24	3.63	.04
L	Middle temporal gyrus	21	-66	-36	-15	3.57	.04

Note. Provided next to each left (L) and right (R) brain region and Brodmann area (BA) are Montreal Neurological Institute (MNI) x, y, and z coordinates in millimeter, where x = right (+) to left (-); y = anterior (+) to posterior (-); z = superior (+) to inferior (-). T values and their corresponding false discovery rate (FDR) corrected P values were derived from a general linear model that predicted voxel-wise grey matter volume from age, sex, and systolic blood pressure (along with their two- and three-way interactions) while controlling for total brain tissue volume (total grey + white matter volume). Sex-by-blood pressure interactions were explained by men, but not women, showing a lower regional grey matter volume as a function of higher systolic blood pressure (see Fig. 1).

Brain areas where higher age predicted lower grey matter volume in 76 men and 58 women

Table 3

Side	Region	BA	MNI coordinates			t	p _{FDR}
			x	y	z		
L	Superior frontal gyrus	11	-19	62	-20	4.53	.04
L	Inferior frontal gyrus	47	-45	19	-9	3.55	.04
R	Inferior frontal gyrus	9	45	10	26	3.91	.04
R	Superior temporal gyrus	22	49	3	-6	3.62	.04
L	Parahippocampal gyrus	28	-19	-19	-24	4.29	.04
R	Insula	13	45	-14	-2	3.70	.04
L	Insula	13	-40	-17	10	3.69	.04
L	Thalamus		-18	-27	-9	4.34	.04
R	Thalamus		2	-21	12	4.31	.04

Note. Provided next to each left (L) and right (R) brain region and Brodmann area (BA) are Montreal Neurological Institute (MNI) x, y, and z coordinates in millimeter, where x = right (+) to left (-), y = anterior (+) to posterior (-); z = superior (+) to inferior (-). T values and their corresponding false discovery rate (FDR) corrected P values were derived from a general linear model that predicted voxel-wise grey matter volume from age, sex, and systolic blood pressure (along with their two- and three-way interactions) while controlling for total brain tissue volume (total grey + white matter volume).

Correlations between grey matter volume and performance on the Trail Making Test (TMT) Part B and the Four-word Short-Term Memory (FWSTM) Test in 76 men and 58 women

Table 4

Grey matter region	TMT Part B ^a		FWSTM ^b			
			5-s Interval		15-s Interval	
	Men	Women	Men	Women	Men	Women
L Supplementary motor area (BA 6)	–0.28 *	0.12	0.29 *	–0.02	0.04	–0.01
L Superior frontal gyrus (BA 8)	–0.17	–0.01	0.19	–0.16	–0.06	0.10
R Anterior cingulate cortex (BA 24)	–0.18	–0.11	0.14	–0.07	–0.07	–0.10
L Middle temporal gyrus (BA 21)	–0.07	–0.09	0.21	–0.02	0.04	–0.11
					0.20	–0.05

Note. Values represent univariate correlations between regional grey matter volume and neuropsychological test performance. Montreal Neurological Institute coordinates for each grey matter region are given in Table 1.

^aTMT part B completion times were adjusted for TMT part A completion times prior to analysis (see Methods section).

^bThe number of correctly recalled items at each interval of the FWSTM were natural log transformed prior to analysis (see Methods section).

* $P < 0.05$.

Table 5

Summary of two-step hierarchical regression analysis for variables predicting men's performance on the Trail Making Test Part B ($n = 76$)

Variable	β	r
<i>Step 1</i>		
Age	0.07	0.12
Educational history	-0.23*	-0.33*
Carotid IMT	0.05	0.09
White matter grade	0.13	0.17
Systolic blood pressure	-0.03	0.05
<i>Step 2</i>		
Age	0.13	
Educational history	-0.17*	
Carotid IMT	0.07	
White matter grade	0.09	
Systolic blood pressure	-0.05	
SMA (BA 6) grey matter volume	-0.28*	-0.28*

Note. Step 1 $R^2 = 0.10$; step 2 $\Delta R^2 = 0.06$, $F = 4.80$, $P < 0.05$. β = standardized regression coefficient; r = univariate correlation; SMA = supplementary motor area. Prior to regression analysis, Trail Making Test Part B completion times were adjusted for Trail Making Test Part A completion times (see Methods section).

Table 6

Summary of two-step hierarchical regression analysis for variables predicting men's correct recall performance at the 5-s interval of the Four-word Short-term Memory Test ($n = 76$)

Variable	β	r
<i>Step 1</i>		
Age	-0.24*	-0.30*
Educational history	0.23*	0.24*
Carotid IMT	0.04	-0.13
White matter grade	-0.11	-0.22*
Systolic blood pressure	-0.12	-0.22
<i>Step 2</i>		
Age	-0.28*	
Educational history	0.17*	
Carotid IMT	0.009	
White matter grade	-0.08	
Systolic blood pressure	-0.02	
SMA (BA 6) grey matter volume	0.24*	0.29*

Note. Step 1 $R^2 = 0.17$; step 2 $\Delta R^2 = 0.05$, $F = 3.99$, $P < 0.05$. β = standardized regression coefficient; r = univariate correlation; SMA = supplementary motor area. Prior to regression analysis, four-word short-term memory scores were natural log transformed.