

Hypertension and the Brain: Vulnerability of the Prefrontal Regions and Executive Functions

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Untreated hypertension negatively affects brain anatomy and cognitive functions, but the effects of medically treated hypertension are unclear. The authors compared 40 middle-age and older adults diagnosed with essential hypertension to demographically matched normotensive peers. Volumes of 7 brain regions and deep and periventricular white-matter hyperintensities (WMH) were measured on magnetic resonance imaging scans. Performance in 4 cognitive domains (perseveration, working memory, fluid reasoning, and vocabulary knowledge) was evaluated. Persons with hypertension had smaller prefrontal cortex and underlying white matter volumes and increased frontal WMH. No group differences were found in other examined brain regions. Among examined cognitive variables, hypertensive patients committed significantly more perseverative errors. Thus, even controlled hypertension may be associated with deficits in brain structure and cognition, warranting further study.

Essential hypertension is a chronic, age-related condition associated with multiple changes in the vascular system (Marin & Rodriguez-Martinez, 1999), and in the vast majority of cases it has no singular identifiable pathological cause (Beevers, Lip, & O'Brien, 2001). The definition of hypertension varies. Although most authorities agree that sustained diastolic pressure greater than 90 mm of mercury (mm Hg) constitutes a cause for diagnosis, the cut-off for the systolic blood pressure varies between 140 mm Hg (Chobanian et al., 2003) and 160 mm Hg (Beevers et al., 2001). In spite of a notable decline in prevalence, still over 20% of adult Americans (and over 55% of those who are older than 70) suffer from hypertension (Burt, Whelton, et al., 1995).

Chronic elevation in blood pressure adversely affects the brain. In otherwise asymptomatic older adults, it increases likelihood of structural brain abnormalities (Carmelli et al., 1999; Salerno et al., 1992; Schmidt et al., 1995; Strassburger et al., 1997; Swan, Carmelli, & La Rue, 1996), especially white matter hyperintensities (WMH; de Leeuw, de Groot, & Breteler, 2000; Raz, 2000). Hypertension is associated with increased risk for Alzheimer-type neuropathology (Kivipelto, Laakso, Tuomilehto, Nissinen, &

Soininen, 2002; Petrovitch et al., 2000), and it is one of the harbingers of vascular dementia (Posner et al., 2002). Although untreated hypertension adversely affects performance on a broad range of cognitive tasks (Boone, Miller, & Lesser, 1993; Brady, Spiro, McGlinchey-Berroth, Milberg, & Gaziano, 2001; M. F. Elias, D'Agostino, Elias, & Wolf, 1995; P. K. Elias, D'Agostino, Elias, & Wolf, 1995; Fahlander et al., 2000; Kilander, Nyman, Boberg, Hansson, & Lithell, 1998; Nilsson et al., 1997; Strandgaard & Paulson, 1995; van Boxtel, Gaillard, et al., 1997; Waldstein et al., 1996; Waldstein, Manuck, Ryan, & Muldoon, 1991), its negative effects may be especially pronounced on the tasks that tap executive functions, speed of processing, and memory. These effects are observed even when hypertensive subjects are compared to control subjects with borderline blood pressure (Harrington, Saxby, McKeith, Wesnes, & Ford, 2000). Sensitivity of the executive functions to hypertension has been demonstrated in nonhuman primates (Moore et al., 2002). As the burden of WMH and cortical shrinkage are linked both to hypertension and to age-related deficits in executive functions (Gunning-Dixon & Raz, 2000; Raz, Gunning-Dixon, Head, Dupuis, & Acker, 1998), they may mediate the effects of hypertension on cognition (de Groot et al., 2002). Indeed, exclusion of medically treated hypertensive participants from a sample can result in a significant reduction in age effects on brain and cognition (Head, Raz, Gunning-Dixon, Williamson, & Acker, 2002).

Although effective medical treatment of hypertension is widely available, it is unclear to what extent treatment alleviates the cognitive impact of hypertension. Limited evidence suggests that persons whose blood pressure is controlled by medication are at lesser risk for cognitive declines than those whose hypertension is undiagnosed or untreated (Dufouil et al., 2001; Fukuda & Kitani, 1995; Tzourio, Dufouil, Ducimetiere, & Alperovitch, 1999). Thus, antihypertensive medication may afford some degree of cognitive protection. However, even treated hypertension may be associated with higher prevalence of white matter abnormalities than ob-

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This study was supported in part by National Institutes of Health Grant AG-11230. Some of the findings reported here were presented at the annual meeting of the Society for Neuroscience, San Diego, CA, November 2001, and the Cognitive Aging Conference, Atlanta, GA, April 2002. We gratefully acknowledge Faith Gunning-Dixon for assistance in developing the WMH measures, and we thank Denise Head, Kristen Kennedy, Adrienne Williamson, Cheryl Dahle, and Amrita Puri for assistance with various aspects of image processing and measurements.

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served in matched normotensive controls (van Swieten et al., 1991).

It is unclear whether specific cognitive functions and their brain substrates known to be vulnerable to the effects of hypertension are indeed protected by antihypertensive treatment. Most of the current knowledge about the effects of hypertension on brain and cognition is based on large population-based studies exemplified by the Framingham Heart Study (P. K. Elias et al., 1995), Boston VA Normative Aging Study (Brady et al., 2001), Honolulu-Asia Aging Study (Launer et al., 2000), Kungsholmen Study (Fahlander et al., 2000), Rotterdam Scan Study (de Leeuw et al., 2002), and the Austrian Stroke Prevention Study (Schmidt et al., 1995). These large-scale projects provided a wealth of information that fueled the rapid advancement of knowledge in the past two decades. However, because of their sheer scope, these studies suffer from several limitations.

First, the definition of the healthy cohort is usually rather broad: both hypertensive and normotensive participants are screened for major neurological diseases and strokes but rarely for cardiovascular and metabolic conditions (e.g., diabetes mellitus) that could confound the effects of hypertension (P. K. Elias et al., 1997). Second, a substantial proportion of the participants (e.g., about 37% in the Framingham Heart Study; P. K. Elias et al., 1995) had obtained less than a high school education, and thus were likely to show below-average levels of cognitive performance regardless of their health status. Third, most of the studies focused on memory and processing speed and failed to include measures of working memory and executive functions, which show significant age-related declines (Head & Raz, 2000; Salthouse, 1994). Fourth, only global indices of brain structural integrity such as ventricular volume, brain volume, or WMH burden were used to assess the effects of hypertension on the brain. Thus, the information provided by large-scale studies needs to be augmented by more focused case-control investigations of selective samples, in which variability on some factors such as treatment history, education, or socioeconomic status is restricted and cognitive and brain measurements are expanded.

To date, only two studies have examined the effects of hypertension on regional differences in brain anatomy (Salerno et al., 1992; Strassburger et al., 1997). In both studies, the groups were not well matched on demographic characteristics; low resolution imaging methods were used; and regions of interest (ROIs) were grossly defined, with gray and white matter combined. The differences attributable to hypertension were found mainly in the size of cerebrospinal fluid cavities, with hypertensive patients demonstrating larger volumes in comparison with normotensive controls.

In the study presented here, we inquired whether treated hypertension has adverse effects on specific brain regions and specific domains of cognitive performance. On the basis of previous research in primates (Moore et al., 2002), we hypothesized that the prefrontal regions and the functions they serve would be differentially vulnerable to the effects of hypertension. Because executive functions in general are sensitive to the effects of hypertension (e.g., Brady et al., 2001) and perseveration is a sensitive index of prefrontal lesions (Stuss et al., 2000), we selected a test of perseverative behavior as an index of prefrontal dysfunction in hypertensive patients. We hypothesized that, unlike global cognitive functions that are sensitive to aging, perseveration might show a

more specific link to hypertension, and that this link would be mediated by declines in the prefrontal regions.

Method

Participants

The data for this study were collected in an ongoing investigation of neuroanatomical correlates of age-related differences in cognition. The participants were paid volunteers who were recruited through advertising in the local media and on an urban university campus. Informed consent was obtained from all subjects, and the study was reviewed and approved by the university's Human Subjects Committee. The prospective participants were interviewed and screened for history of cardiac, neurological, and psychiatric conditions; head trauma with loss of consciousness; alcohol and drug abuse; thyroid disease; and diabetes mellitus. Subjects with auditory and visual impairments (including color blindness) did not participate in the study. All participants were screened for dementia and depression with a modified Blessed Information–Memory–Concentration Test (Blessed, Tomlinson, & Roth, 1968), and Geriatric Depression Questionnaire (Radloff, 1977) with cut-off scores of 30 and 15, respectively. Only strongly right-handed persons (75% and above on the Edinburgh Handedness Questionnaire; Oldfield, 1971) were included in this sample. Four hundred thirty persons met the outlined criteria. Among those, 40 participants (24 women and 16 men) reported a history of hypertension that was diagnosed by their physicians. The validity of self-reported diagnosis of hypertension has been demonstrated in non-Hispanic whites and non-Hispanic black women, a population similar to the source of this sample (Vargas, Burt, Gillum, & Pamuk, 1997). Moreover, the fact that all subjects with self-reported hypertension were taking at least one antihypertensive medication supports the validity of the diagnostic group assignment.

The sample description is presented in Table 1. The 40 participants with diagnosis of essential hypertension were matched with 40 normotensive controls on sex and ethnicity (1 hypertensive and 1 control were African-American women), age (± 3 years), and education (± 3 years). The groups ($n = 40$ each) had virtually identical mean age (with an age range of 30–77 years), Blessed scores, and education (range = 12–21 years). There were no sex differences in age (60.85 ± 10.09 years for women vs. 62.72 ± 13.04 years for men), $t(78) < 1$, or education (15.38 ± 2.63 years for women vs. 15.44 ± 2.59 years for men), $t(78) < 1$.

Medications. All participants who had been diagnosed with hypertension were treated with various antihypertensive medications prescribed and monitored by their physicians. The breakdown by the type of medication is presented in Table 1. The most frequently administered type of antihypertensive drug in this sample was calcium channel blockers (CCBs). Some participants ($n = 8$) were taking two medications, but none was taking loop diuretics that are usually prescribed for hypertension accompanied by congestive heart failure or renal disease. Because in some cases antihypertensive drugs can interfere with the general level of arousal, the experimenters paid special attention to fluctuations in the alertness of the participants during performance.

Blood pressure measures. Because the participants were drawn from multiple studies undertaken in our laboratory, blood pressure measures were available only for some of them ($n = 44$, 55% of the total sample), with the proportion of assessed participants not differing between the groups. A mercury sphygmomanometer (Model 12–525; Country Technology, Gays Mills, WI) with a brachial cuff was used to obtain systolic and diastolic blood pressure before each cognitive testing session began. Three measures on 3 different days were obtained from subjects, who were seated in a comfortable chair in a climate-controlled office. The comparison of the available blood pressure readings (Table 1) showed that, on average, the normotensive group maintained normal systolic and diastolic blood pressure. Four nominally normotensive and 9 hypertensive participants had high-normal blood pressure, that is, Stage 1 hypertension: systolic or

Table 1
Sample Description and Comparison of Hypertensive and Normotensive Groups on Demographic Variables

Variable	Group		Comparison test <i>p</i>
	Normotensive	Hypertensive	
Age (years)	61.63 ± 11.25	61.56 ± 11.68	.98
Sex (male:female ratio)	2:3	2:3	1.00
Education (years)	15.65 ± 2.52	15.15 ± 2.69	.39
Mean (±SD) Blessed score	31.88 ± 1.52	31.85 ± 1.51	.94
% with blood pressure measures	50	60	.37
Mean (±SD) systolic blood pressure (mm Hg)	126.00 ± 13.15	137.83 ± 14.64	.01
Range	100–152	115–178	
Mean (±SD) diastolic blood pressure (mm Hg)	80.00 ± 9.27	84.56 ± 9.63	.12
Range	63–104	70–103	
% with high normal blood pressure	20.0	37.5	.21
% with high blood pressure	5.0	12.5	.39
Medication			
CCB		40%	
Beta blockers		29%	
K ⁺ -sparing diuretics		22%	
ACE inhibitors		22%	
Miscellaneous vasodilators		7%	

Note. The *p* values, unadjusted for the number of comparisons, are for two-sample *t* test or chi-square, whichever was appropriate. CCB = calcium channel blockers; ACE = angiotensin converting enzyme.

diastolic readings that require no medical intervention but trigger a recommendation for lifestyle modification and a short-term follow-up (Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [JNC], 1997). One nominally normotensive and 3 hypertensive participants exhibited blood pressure readings that fell in the range of Stage 2 hypertension. None of the participants reached the levels of hypertension (180 mm Hg systolic or 110 mm Hg diastolic) at which prompt medical intervention is recommended (JNC, 1997). The hypertensive participants, on average, had high-normal systolic, but not diastolic, blood pressure. The group difference in systolic blood pressure was significant, whereas the difference in diastolic blood pressure was not. However, no group differences in variance of blood pressure measures were noted. The participants from whom blood pressure measures were obtained were not selected by any criteria. They just happened to be admitted to the study after a decision was made to include blood pressure measures in the protocol. They did not differ from those whose blood pressure was not assessed on any demographic or cognitive index ($ps > .25$) and were deemed representative of the total sample. The obtained measures support the validity of the assumption that the participants in the control group were indeed normotensive and that hypertensive participants evidenced reasonably successful (albeit not complete) control of their hypertension.

MRI Protocol

Imaging was performed on a 1.5-T Signa scanner (General Electric, Milwaukee, WI). All volumetric measures were performed on the reformatted images acquired using T1-weighted 3-D spoiled gradient recalled acquisition sequence with 124 contiguous axial slices. The acquisition parameters were as follows: echo time (TE) = 5 ms, repetition time (TR) = 24 ms, number of excitations (NEX) = 1, field of view (FOV) = 22 cm, acquisition matrix = 256 × 192, slice thickness = 1.3 mm, and flip angle = 30°, except for three pairs of subjects whose images were acquired with FOV = 24 cm. The WMH volumes were estimated from T2-weighted axial images from an axial double-echo T2- and proton-density (PD)-weighted fast spin echo (FSE) sequence. The FSE sequence parameters were TR = 3,300 ms, effective TE = 90 ms for T2 slices and 18 ms for proton density images, FOV = 20 × 20 cm, matrix = 256 × 256, slice

thickness = 5 mm, and interslice gap = 2.5 mm. Between 18 and 20 T2-weighted axial slices per participant were available. All MR scans were examined for space-occupying lesions, and all probable cases were evaluated by a neuroradiologist (James D. Acker).

Quantification of WMH. Because the limited number of relatively thick slices and lack of interslice contiguity would have caused distortion at realignment, the FSE T2-weighted images were not realigned. The axial slices were divided into frontal, temporal, parietal, and occipital ROIs, described below and shown in Figure 1.

Hyperintense regions, defined as circumscribed areas of increased signal intensity within the white matter, were identified and measured on axial slices of the T2-weighted images, beginning at the most inferior slice on which the inferior horns of the lateral ventricles were present. Because of the difficulty in distinguishing WMH from emerging sulci and blood vessels in the superior convexity, the last slice on which WMH were quantified was located three slices below the vertex. All identifiable WMH—periventricular and deep white matter—were included. A total WMH volume was obtained by summing the volumes of hyperintensities from all of the ROIs and multiplying by the sum of the interslice distance and slice thickness. Because the distinction between gray and white matter is clearer on the PD-weighted images, the latter were used as reference in making decisions about lesion location and neuroanatomical boundaries.

Interrater reliability was assessed by the intraclass correlation formula for two random raters (ICC[2]; Shrout & Fleiss, 1979), from measures conducted by two trained operators who traced a random sample of 10 brains. Intrarater reliability of the WMH volumes was also assessed from the data collected by one rater who traced 10 randomly chosen brains on two separate occasions, 7 days apart. For practical and logistic reasons, only one experimenter (Karen M. Rodrigue), who was unaware of the subjects' exact age, sex, and diagnosis, performed all WMH measurements reported here.

Frontal WMH. On ventral slices, the frontal region included the region anterior to the lateral sulcus. When the central sulcus emerged on dorsal slices, it served as the caudal boundary. The interrater reliability of this measure was ICC(2) = .94.

Temporal WMH. On ventral slices, the anterior boundary of the temporal region was the lateral fissure, and the temporal–occipital incisure

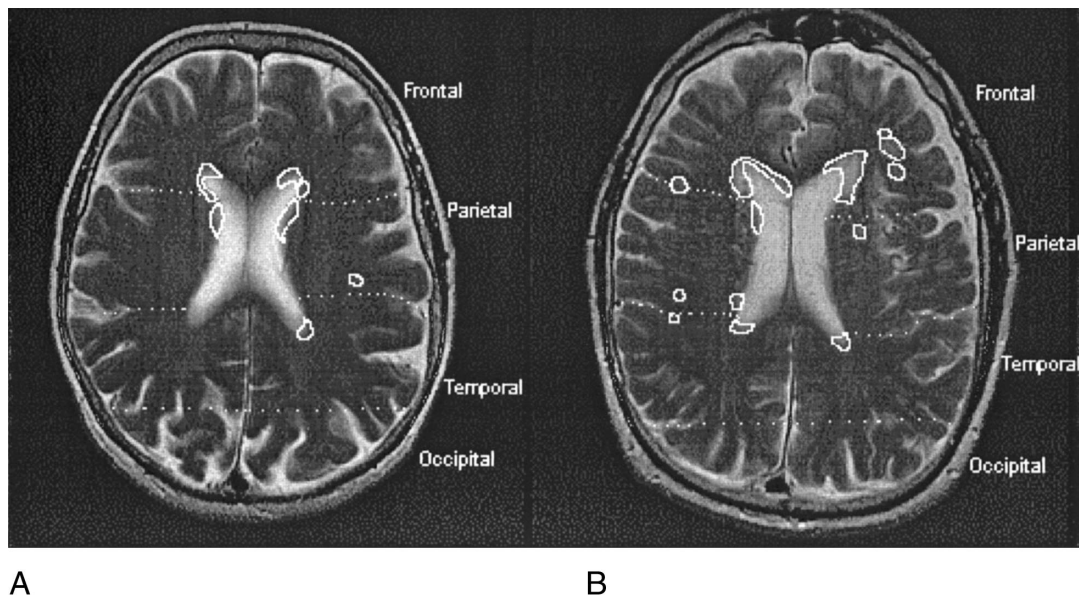


Figure 1. Examples of traced white-matter hyperintensities of a typical matched pair of 77-year-old normotensive (A) and hypertensive (B) subjects.

served as the posterior boundary. On superior slices, the parieto-occipital sulcus appeared medially, and a horizontal line was drawn from the parieto-occipital sulcus to the lateral surface of the cortex to form the boundary between the occipital and temporal regions. The temporal WMH were traced until the slice on which the superior temporal gyrus could no longer be seen (usually the slice inferior to the last slice of the corpus callosum). This measure had an interrater reliability of $ICC(2) = .91$.

Parietal WMH. The parietal ROI began on the most inferior slice where the central sulcus could first be identified. On ventral slices, the central sulcus served as the anterior boundary, and the lateral fissure was the posterior boundary (separating the parietal from temporal regions). On dorsal slices (beginning with the last slice on which the corpus callosum was present), all white matter posterior to the central sulcus was included in the parietal region. The interrater reliability was $ICC(2) = .92$.

Occipital WMH. The occipital region included white matter posterior to the temporal-occipital fissure (laterally) and the parieto-occipital sulcus (medially). The interrater reliability of that measure was $ICC(2) = .89$.

Total WMH. Measurements of WMH from frontal, temporal, parietal, and occipital regions were summed to obtain total WMH. The interrater reliability of the combination was $ICC(2) = .96$.

Volumetric image analysis. The MR images were aligned and resliced into contiguous 1.5-mm coronal sections with the public domain software BrainImage 2.3.3 (Reiss, Hennessy, Rubin, Beach, & Subramaniam, 1995). The previously published procedure (Raz et al., in press) was used to standardize brain position and correct undesirable effects of head tilt, pitch, and rotation. The ROIs were measured with NIH Image software (Version 1.60; Rasband, 1996), and the volumes were computed by multiplying the sum of areas by slice thickness. The reliability coefficients ranged between .93 and .99, with a median $ICC(2)$ of .96. The rules of ROI demarcation and tracing were previously published elsewhere (Raz et al., 1997; Raz et al., in press) and are presented here only in abbreviated form.

The intracranial volume (ICV) was measured on every eighth coronal slice of the whole brain volume. The ICV included the volume between the left- and rightmost ventral points of the inner table of the cranium, and between the orbits and the last slice on which the brain was visible. The volume of the prefrontal cortex (PFC) was computed from 10–13 coronal slices; it included both the lateral PFC and orbital frontal cortex and

covered all or parts of Brodmann areas (BA) 8, 9, 10, 11, 45, 46, and 47. The total volume of the PFC, as defined by these rules, was computed by summing lateral PFC and orbital frontal cortex volumes. The prefrontal white matter was measured on the same coronal slices as the PFC and included all white matter adjacent to the PFC. The hippocampal formation was measured on a series of 19–25 slices. To avoid confounding age-related expansion of the inferior horns of the ventricles with demarcation of the amygdala-hippocampus border, we used the mammillary bodies as the rostral boundary of the hippocampal formation. Thus, a small anterior portion of the structure was excluded. The visual (pericalcarine) cortex was defined as the cortical ribbon lining the calcarine sulcus. This ROI covered a part of the primary visual cortex (BA 17) located along the banks of the calcarine fissure. The fusiform gyrus spanned temporal and occipital lobes, excluding the lingual sulcus and covering BA 37 and BA 19. The inferior parietal lobule was measured on the coronal slices located between the posterior commissure and the last slice on which the splenium of the corpus callosum could be observed, and included a portion of BA 40. The white matter adjacent to the inferior parietal ROI was traced as an ROI complementary to the cortical region described above.

Cognitive Tasks and Procedures

The following cognitive tasks were administered to each participant individually by technicians who were blind to the participant's medication status and diagnosis of hypertension. Because participants from different studies were combined for this report, the order of task administration varied depending on the schedule of a particular study.

Executive functions task. The computerized version of the Wisconsin Card Sorting Task (WCST; Neuroscan Corp., Herndon, VA) was administered to all participants individually. The participant's task was to sort cards displayed on a computer screen. The cards contained geometric designs and could be sorted into categories by shape, color, or number of the design. Participants were asked to match a card that appeared in the lower right corner of the computer screen with one of the four cards displayed at the top of the screen. The participants were told that the computer would provide feedback about the correctness of their decision,

but that the examiner could not give them any additional information about their performance on the task.

The WCST provides a number of indices intended to measure executive functions: the total number of errors, the number of perseverative errors, the number of perseverative responses, the number of categories attained, and the learning-to-learn index (Heaton, Chelune, Talley, Kay, & Curtis, 1993). Although believed to be useful in individual clinical assessment, these indices are highly correlated, and some of them have limited variability and restricted range of scores. For the purposes of assessing an exemplary executive function—the ability to abandon a reinforced response in favor of a novel and more adaptive one—the average of the standardized number of perseverative responses and perseverative errors residualized on the total number of errors to control for overall level of performance was used as the index of performance. The median long-term test–retest reliability of the WCST across multiple studies is estimated at .75 (Pennington, Bennetto, McAleer, & Roberts, 1996).

Working memory. The participants performed two verbal working memory tasks: Computation Span (CSPAN) and Listening Span (LSPAN; Salthouse, Mitchell, Skovronek, & Babcock, 1989), and a nonverbal working memory task: Size Judgment Span (Cherry & Park, 1993). Both span tasks measure the ability for simultaneous storage and processing of verbal information and are very similar in structure, administration, and scoring. In CSPAN, the subject is asked to solve simple arithmetic problems while simultaneously remembering the last digit in each problem. In LSPAN, the subjects listen to simple sentences. After each sentence, they are asked to answer a question about its content and to report its final word. The Absolute Span, which is calculated by summing the number of correct items across blocks of trials on which the participant answered all of the items correctly, was the index of choice on both LSPAN and CSPAN because it produces a reasonably wide range of scores and is not particularly prone to capitalization on chance (Engle, Cantor, & Carullo, 1992). On Size Judgment Span, participants were read aloud lists of objects and animals and were asked to repeat each list with the items arranged in ascending order by size. The score on this test was the cumulative number of correct trials. Scores on each of the three tests were standardized and averaged into a working memory composite index.

General cognitive functions (fluid and crystallized). The Cattell Culture-Fair Intelligence Test (CFIT) Forms 2A and 3A combined (Cattell & Cattell, 1973) were used as a measure of fluid reasoning. This is essentially a test of nonverbal reasoning composed of four subtests per form (eight subtests total). Each subtest consists of 10–14 items tapping different domains of nonverbal abstract reasoning, including detection of similarities in designs, completing matrices according to specific rules, and solving nonverbal syllogisms. In all problems, the participant has to derive the rule required to solve the problem. The test is timed, with 2.5–4.0 min allowed for completion of each subtest (a total of 12 min). The index of performance is the number of total correct items across the eight subtests.

The Vocabulary Test from the Educational Testing Service Kit of Factor-Referenced Tests (Ekstrom, French, Harman, & Dermen, 1976) served as an index of crystallized abilities. This multiple-choice test of vocabulary knowledge was constructed by combining the first halves (42 items altogether) of two vocabulary tests (Vocabulary V-2 and Extended Vocabulary V-3). In our experience, all of our participants (young or old) have completed this test within the allocated time limit. The performance index was the number of correct items minus 25% of incorrect items (correction for guessing).

Results

Descriptive Statistics and Data Conditioning

Before the data were submitted to the analyses, the distributions were examined for outliers and gross deviations from normality. The examination revealed that the distributions of WCST errors

and WMH volumes were exponential, with rare high scores outweighed by considerably more frequent low-end scores. To alleviate the skew, these variables were transformed by means of a natural logarithms function with 1 added to its argument to offset the zero scores. The correlation matrix of the raw cognitive scores revealed that the three span measures were moderately correlated in the hypertensive group ($r = .46-.57, ps < .001$), and LSPAN correlated with CSPAN in the normotensive group as well ($r = .51, p < .001$). As a result of these associations among the tests and the lack of specific hypotheses concerning each of the measured types of working memory, we converted all three scores into standardized Z-scores based on the whole sample means and standard deviations and combined them in a composite working memory score. Perseveration score was a standardized residual from a regression of the number of perseverative errors on the total number of errors on the WCST. The scores on the CFIT and vocabulary tests were used in their raw format. The means and standard deviations of the regional brain volumes, regional volumes of the WMH, and raw cognitive scores for the two groups are presented in Table 2.

Although the diagnostic group's mean intracranial volumes did not differ ($1,861.05 \pm 177.00 \text{ cm}^3$ for normotensive vs. $1,789.41 \pm 206.71 \text{ cm}^3$ for hypertensive), $t(78) = 1.60, ns$, and the intracranial volume did not correlate with age ($r = .16, ns$), the expected sex differences were apparent, $t(78) = 5.99, p < .001$. To control for sex differences in cranial size, all regional volumes were adjusted for the ICV by using the analysis of covariance approach. The adjusted volumes were computed from a linear equation: $\text{Volume}_{adj_i} = \text{Volume}_{raw_i} - b(\text{ICV}_i - \text{Mean ICV})$ for each subject i , where Volume_{adj_i} is adjusted volume of a given ROI, Volume_{raw_i} is raw volume of that ROI, b is a slope of ROI volume regression on ICV, and Mean ICV is a sample mean of the ICV. For each variable, the homogeneity of regression slopes (i.e., absence of Sex \times ICV interaction) was ascertained to allow the use of a common slope for both sexes.

A general linear model approach was used in all analyses reported below. In these analyses, ROIs, lobes, and types of WMH (deep white matter vs. periventricular) served as categorical repeated measure variables. Diagnosis (Dx) was a categorical independent variable, age (recentered at the total sample mean) was a continuous independent variable, and sex (a categorical variable) was entered as a covariate. Each model was checked for violation of the assumption of homogeneity of regression slopes of the dependent variables on the continuous predictor (age), for all levels of the categorical variables. The significance of interactions of age, Dx, and sex were examined; if they were found nonsignificant, the interactive terms were removed from the models. The p levels for all interaction effects that involved the repeated measures were adjusted by using Huynh–Feldt correction. All analyses were repeated on a subsample of participants for whom blood pressure measures were available, and on a sample excluding 4 participants who exhibited high blood pressure. The objective was to verify that the observed pattern of results was not dependent on the presence of incorrectly classified normotensive and hypertensive participants.

Examination of the WMH distribution by regions revealed that only 15 (19%) of the participants exhibited occipital WMH. Individuals with occipital WMH were evenly distributed between the diagnostic groups: 7 among the control subjects and 8 among the

Table 2
Descriptive Statistics for Brain Measures and Cognitive Variables

Variables	Group			
	Control		Hypertension	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Brain				
Prefrontal cortex	27.00	3.14	25.06	2.83
Prefrontal white matter	39.18	5.76	36.11	6.05
Fusiform cortex	18.01	2.15	17.80	2.00
Inferior parietal cortex	12.72	3.06	11.95	2.49
Inferior parietal white matter	11.07	2.93	10.44	2.37
Hippocampus	6.43	0.75	6.57	0.69
Primary visual cortex	5.38	1.01	5.13	0.75
Frontal WMH	3.54	5.25	4.86	4.76
Temporal WMH	3.41	4.33	3.05	3.20
Parietal WMH	1.74	3.30	1.62	2.27
Occipital WMH	0.15	0.45	0.25	0.63
Cognition				
CFIT raw score	54.98	9.02	52.68	8.85
Vocabulary	29.36	7.04	26.77	7.04
Computation Span	15.13	11.84	12.68	8.22
Listening Span	20.73	9.04	19.45	8.50
Size Judgment Span	8.68	1.38	9.08	1.33
WCST, perseverative responses	22.75	15.63	33.58	24.88
WCST, perseverative errors	19.75	12.40	28.15	19.27
WCST, total errors	38.03	21.17	44.85	22.34

Note. All volumes are in cubic centimeters. WMH = white matter hyperintensities; CFIT = Cattell Culture-Fair Intelligence Test; WCST = Wisconsin Card Sorting Test.

hypertensive subjects. As a result of such sparseness of the data, we used only three regional WMH measures in the linear model analyses: frontal, temporal, and parietal.

Regional Brain Volumetry, Hypertension, and Age

The magnitude of the differences between the diagnostic groups varied across ROIs, as indicated by a marginally significant $Dx \times ROI$ interaction, $F(6, 456) = 2.84, p = .05$. The magnitude of age-related differences in regional volumes also varied across the examined regions, as suggested by an $ROI \times Age$ interaction, $F(6, 456) = 7.12, p < .01$. In addition, there were overall volume differences between the hypertensive and normotensive groups, $F(1, 76) = 4.06, p < .05$, and a significant age effect, $F(1, 76) = 16.30, p < .001$.

To interpret the significant interactions, we examined simple effects using univariate linear models with the predictors that featured in the general model. The results of these analyses revealed that the PFC volume and the volume of the prefrontal white matter exhibited significant effects of age, $F(1, 76) = 10.53, p < .01$; $F(1, 76) = 18.17, p < .001$, respectively, and diagnosis, $F(1, 76) = 7.80, p < .01$; $F(1, 76) = 6.24, p < .05$, respectively. The hippocampus and the fusiform gyrus evidenced significant age-related reduction in volume, $F(1, 76) = 13.76, p < .001$; $F(1, 76) = 5.81, p < .05$, respectively, but no hypertension-related differences ($F < 1$). The primary visual and the inferior parietal

cortical volumes and the parietal white matter showed neither age-related nor hypertension-related differences ($Fs < 1$).

Removal of 4 participants with high blood pressure, regardless of their diagnostic classification, did not alter the results, except for boosting the $Dx \times ROI$ interaction effect, $F(2, 432) = 3.48, p < .05$. However, when the analyses were repeated on the subsample of 44 participants with known blood pressure, the overall effect of hypertension disappeared ($F < 1$), and the $Dx \times ROI$ interaction became nonsignificant, $F(6, 240) = 2.11, p < .12, ns$ (although $p < .05$ without Huynh-Feldt correction). The effect of hypertension on the prefrontal cortical volume remained significant, $F(1, 40) = 4.37, p < .05$, but hypertension-related differences in the prefrontal white matter volume were eliminated ($F < 1$).

WMH Volume

Diagnosis of hypertension was not linked to differences in overall WMH volume ($F < 1$), but the magnitude of the diagnosis-related difference varied across the regions, as indicated by a significant $Lobe \times Dx$ interaction, $F(2, 152) = 6.04, p < .01$. The overall WMH volume was associated with age, $F(1, 76) = 37.63, p < .001$, and strength of that association also differed across the lobes and types of WMH, as indicated by a significant $Age \times ROI \times Type$ interaction, $F(2, 152) = 8.61, p < .001$. Other triple interactions were not significant ($F < 1$). A significant $Type \times$

Lobe interaction, $F(2, 152) = 45.86, p < .001$, indicated that WMH volume differed across locations depending on the type.

The analyses of simple effects revealed that frontal WMH volume differed between the diagnostic groups, $F(1, 76) = 7.31, p < .01$, and significantly increased with age, $F(1, 76) = 41.18, p < .001$. Temporal and parietal WMH volume showed substantial age differences, $F(1, 76) = 39.02, p < .001; F(1, 76) = 14.93, p < .001$, respectively, but no hypertension-related increase ($F < 1$). The volume of frontal and temporal periventricular WMH was equal, $t(78) = -.44, ns$, and both exceeded the volume of the parietal periventricular WMH, $t(78) = 12.17$ and 8.45 for frontal and temporal lobes, respectively, $ps < .001$ (Bonferroni-adjusted). Deep white matter WMH occupied greater volume in the frontal lobe than in the temporal lobe, $t(78) = 6.92, p < .01$ (Bonferroni-adjusted), and parietal, $t(78) = 5.46, p < .01$ (Bonferroni-adjusted), regions, whereas parietal deep WMH burden was larger than that of the temporal lobe, $t(78) = 3.67, p < .05$ (Bonferroni-adjusted).

The decomposition of the triple interaction was conducted by comparing the magnitude of age–WMH volume correlations broken down by lobes and type of lesions (periventricular vs. deep-white matter) with Steiger's Z^* statistic (Steiger, 1980). It revealed that the same magnitude of age differences was observed within the examined lobes for periventricular and deep white matter lesions (for all comparisons, $p > .20$). However, the strength of age-related differences in periventricular WMH burden varied across the lobes, with the frontal and temporal lobes showing stronger links ($r = .54$ and $r = .53, p < .001$, respectively) compared with the parietal lobe ($r = .25, p < .05$). Both differences were significant, $Z^* = 3.02$ and $2.22, p < .01$ and $p < .05$, respectively. Neither the exclusion of 4 participants with high blood pressure nor restriction of the sample to participants who had actual measures of blood pressure altered the observed pattern of results, although significance levels of some effects were reduced.

Influence of Illness Duration and Type of Medication

Within the hypertension group, the influence of illness duration was examined in linear models, in which the dependent variable—regional volume of brain tissue or of WMH—was predicted by age, sex, and duration of illness (time since diagnosis). To alleviate the influence of extreme values, a logarithmic transformation was applied to illness duration. The continuous variables (age and illness duration) were recentered at their group means. The results of these analyses indicate that in addition to (and independently of) the above-mentioned effect of age, longer duration of hypertension was associated with increased WMH burden, $F(1, 36) = 5.36, p < .05$, but not with regional cortical volumes, $F(1, 36) = 1.92, ns$. Analyses on a restricted sample of participants with actual blood pressure measures produced no change in the pattern of results for WMH. However, in hypertensive participants with ascertained blood pressure ($n = 24$), longer duration of illness was associated with smaller regional cortical volumes, $F(1, 20) = 4.78, p < .05$. Grouping by medication type produced no significant differences, and people who took two antihypertensive medications did not differ on any of the examined brain measures from those who took only one.

Cognitive Performance

A mixed linear model similar to those that were used in the analyses of brain measures was applied to the cognitive data. In these analyses, the repeated measures were test scores on CFIT, vocabulary, standardized working memory composite, and perseverative errors on the WCST residualized on total errors; the predictors were age, sex, and diagnosis.

The general model analysis revealed significant Test \times Dx, $F(3, 248) = 4.77, p < .01$, and Test \times Age, $F(3, 248) = 12.27, p < .001$, interactions. The main effect of age was significant, $F(1, 76) = 4.60, p < .05$, whereas the main effect of hypertension was not ($F < 1$). The interactions were decomposed with univariate linear models. The analyses revealed that only the perseveration index evidenced a significant effect of diagnosis, $F(1, 76) = 5.11, p < .05$. The group differences in working memory ($F < 1$); fluid reasoning, $F(1, 76) = 1.77, ns$; and vocabulary, $F(1, 76) = 2.78, ns$, were not significant. When compared with the nominally normotensive controls, the hypertensive group showed a more than 42% increase in perseverative errors but less than 18% increase in total errors (see Table 2). The age differences were significant in working memory, $F(1, 76) = 17.72, p < .001$, and fluid reasoning, $F(1, 76) = 23.74, p < .001$, but not in perseveration index ($F < 1$) or vocabulary scores, $F(1, 76) = 1.69, ns$.

No differences related to the type of medications were observed. Removal of 4 participants with high blood pressure did not influence the results, except for reducing the significance of the main effect of age ($p < .06$). Reanalysis on a subsample of participants with blood pressure measures ($n = 44$) did not affect the results.

Examination of the associations between cognitive variables, regional brain volumes, and WMH burden (see Table 3) revealed the expected negative correlations of the measures of fluid reasoning and working memory with age and the lack of association between age and vocabulary scores. However, perseveration was not associated with any of the variables except for a small though significant correlation with the deep WMH in the frontal lobe. The fluid intelligence index was lower in people with smaller hippocampi, prefrontal cortices, and prefrontal white matter, and those who had greater periventricular frontal and temporal WMH and frontal deep WMH. Working memory composite followed roughly the same pattern, although it was not at all related to the periventricular WMH load. However, unlike the perseverative errors residualized on total errors, the raw counts of perseverative and total errors on the WCST correlated with age ($r = .40$ and $.42, ps < .001$) and prefrontal volume ($r = .25$ and $.20, p < .05$ and $p < .07$, respectively).

In the hypertensive group, duration of illness was significantly associated with decrements in performance on some of the tests, as indicated by a significant Test \times Years of Illness interaction, $F(3, 108) = 3.05, p < .05$. Although there was an overall effect of age on test performance, $F(1, 36) = 4.12, p < .05$, the extent of age-differences varied across the tests, as indicated by an Age \times Test interaction, $F(3, 108) = 6.54, p < .001$. Examination of simple effects revealed that whereas perseveration on WCST increased ($r = .40, p < .01$) and fluid intelligence performance decreased ($r = -.36, p < .05$) with longer duration of hypertension, vocabulary ($r = .07, ns$) and working memory ($r = -.15, ns$) performance were unrelated to illness duration. Age differences in fluid intelligence ($r = -.57, p < .001$) and working memory ($r =$

Table 3
Correlations Between Age, Regional Brain Volumes, White Matter Hypertension Burden, and Cognitive Performance Indices

	Age	PFC	FW	HC	VC	FG	IP	IPW	FPWMH	TPWMH	PPWMH	FDWMH	TDWMH	PDWMH	CFIT	WCST	WM
PFC	-0.30																
FW	-0.40	0.69															
HC	-0.33	0.34	0.37														
VC	-0.14	0.19	0.26	0.11													
FG	-0.25	0.29	0.44	0.40	0.11												
IP	-0.17	-0.05	0.01	0.07	0.03	0.34											
IPW	-0.05	-0.06	-0.02	0.04	0.03	0.27	0.94										
FPWMH	0.54	-0.44	-0.33	-0.31	-0.03	-0.16	-0.07	-0.02									
TPWMH	0.53	-0.28	-0.31	-0.22	-0.16	-0.16	-0.03	0.05	0.49								
PPWMH	0.25	-0.03	-0.08	-0.15	-0.10	-0.17	0.10	0.05	0.54	0.40							
FDWMH	0.46	-0.34	-0.36	-0.19	-0.17	-0.12	-0.04	-0.03	0.56	0.56	0.35						
TDWMH	0.36	-0.27	-0.21	0.05	-0.12	-0.03	0.00	0.05	0.44	0.35	0.25	0.54					
PDWMH	0.37	-0.22	-0.28	-0.10	-0.16	-0.14	-0.04	0.00	0.49	0.35	0.40	0.80	0.52				
CFIT	-0.47	0.28	0.45	0.31	0.38	0.18	0.08	0.04	-0.22	-0.23	-0.02	-0.34	-0.02	-0.25			
WCST	0.06	-0.16	0.02	0.06	0.05	0.02	0.07	0.09	0.13	0.07	0.17	0.28	0.05	0.19	0.02		
WM	-0.44	0.21	0.37	0.22	0.27	0.18	0.26	0.19	-0.03	0.08	0.09	-0.21	-0.04	0.03	0.45	0.02	
Vocabulary	0.14	0.21	0.23	-0.03	0.16	-0.04	-0.07	-0.07	0.12	0.16	0.08	0.04	0.05	0.06	0.23	0.02	0.09

Note. Critical values of $r = .22$ for $p < .05$, $.29$ for $p < .01$, and $.37$ for $p < .001$. PFC = prefrontal cortex; FW = frontal white matter; HC = hippocampus; VC = visual cortex; FG = fusiform gyrus; IP = inferior parietal cortex; IPW = inferior parietal white matter; FPWMH = frontal periventricular white matter hypertensities; TPWMH = temporal periventricular white matter hypertensities; PPWMH = parietal periventricular white matter hypertensities; FDWMH = frontal deep white matter hypertensities; TDWMH = temporal deep white matter hypertensities; PDWMH = parietal deep white matter hypertensities; CFIT = Cattell Culture-Fair Intelligence Test; WCST = Wisconsin Card Sorting Test; WM = Wechsler Memory Scale. All WMH volumes are log-transformed.

-.63, $p < .001$) exceeded those in perseveration ($r = .21$, ns) and vocabulary ($r = .06$, ns).

Discussion

The results of this study confirm that people who receive a diagnosis of hypertension and have no other major disease have elevated WMH burden and reduced volume of brain tissue. However, those differences are not global. They appear to be confined to the frontal regions of the brain, and more specifically, to the PFC and the underlying white matter. Those localized brain differences are accompanied by cognitive differences that suggest isolated vulnerability of some executive functions to hypertension. Although those findings would not be surprising in people with untreated hypertension, their presence in a group of high-functioning, educated, and otherwise healthy adults is alarming. Notably, when the presence of participants with elevated blood pressure in both groups was taken into account, the observed differences did not diminish but, if anything, became even stronger. These findings refine the conclusions of a recent study in which even relatively small increases in blood pressure may have been associated with generalized brain atrophy (Goldstein, Bartzokis, Guthrie, & Shapiro, 2002). Apparently, hypertension exerts its most significant effects on the regions that have been characterized by increased vulnerability to aging (i.e., the PFC; Raz 2000).

In accord with a recent report (de Leeuw et al., 2002), hypertension-related differences in WMH burden were observed in periventricular and deep white matter areas alike. However, age differences in the WMH volumes were not equally strong across the compartments and lobes. Within the hypertensive group, we found evidence of a dose-response relationship between illness duration and the indicators of cerebral and cognitive integrity. Specifically, longer time elapsed since diagnosis was associated with greater frontal WMH burden, marginally smaller prefrontal cortices, and lesser ability to resist perseveration.

In this sample, we found no interactions between age and diagnosis of hypertension. Thus, we replicated neither a progressive increase in brain abnormalities in older hypertensive patients (Strassburger et al., 1997), nor increased prevalence of WMH (de Leeuw et al., 2002) and greater cognitive deficits in younger hypertensive patients (Waldstein et al., 1996). Beside the fact that interaction effects are notoriously difficult to replicate, these discrepancies may stem from the differences among the samples. In this study, we had no participants in their 80s and 90s (i.e., persons found to be at lower risk for WMH by de Leeuw et al. 2002), probably as a result of differential survival. Most of the participants were women, in contrast to the all-male sample (Waldstein et al., 1996) and mostly male hypertensive group (Strassburger et al., 1997) in other studies. The participants in our study maintained reasonably good control of their blood pressure by continuing their medication regimen, in contrast to an acute off-medication sample (Strassburger et al., 1997).

We found no links between a specific type of antihypertensive medication and differences in neuroanatomy and cognitive performance, in spite of the fact that most medications (beta-blockers, CCBs, and diuretics, but not ACEs) exert some adverse effects on selected areas of cognition (Jonas, Blumenthal, Madden, & Serra, 2001). The reasons may be the lack of statistical power and the

highly selective nature of the sample. Previous studies that reported adverse effects of antihypertensive agents (e.g., CCBs) on cognitive performance (Maxwell, Hogan, & Ebly, 1999) included persons with a history of stroke and diabetes. Although the influence of those conditions was statistically controlled, such controls could have been insufficient to alleviate the negative impact of cerebrovascular disease and the variables that are associated with it but remain unspecified in statistical models. In contrast to the CCBs, no adverse effects of beta-blockers on verbal memory or speed of information processing were found (McCaffrey, Ortega, Orsillo, Haase, & McCoy, 1992; Perez-Stable et al., 2000). Some antihypertensive medication may even retard cognitive declines (M. F. Elias, 1998; Jonas et al., 2001). In contrast to a sizeable (though contradictory) literature on antihypertensive medication and cognition, there is no evidence to suggest that effects of antihypertensive medication may be responsible for alterations in brain structure. However, it would be prudent to assume that because of the cross-sectional design of the study, it is impossible to ascertain that the observed differences did not result from antihypertensive treatment.

Mechanisms of the Observed Differences

Although it is unclear what mechanisms may account for the reported findings, the extant literature offers some plausible, albeit speculative, explanations. First of all, one must take note of the distribution of cerebral blood supply. The evidence suggests that cerebral white matter is the least irrigated compartment of the brain, and as such it may be more vulnerable than the gray matter to the effects of ischemia and hypoperfusion (Brown, 2000; Pantoni & Garcia, 1997). Moreover, vasodilatory capacity of the prefrontal white matter is even lower than that of the white matter in other brain regions (Brown, 2000). The location of the lateral prefrontal regions examined in this study at the downstream of the middle cerebral artery also places them at elevated risk of subclinical ischemia. Hypertension is associated with reduced ability to regulate vasomotor response (Bakker et al., 1999), and there is a general reduction in regional cerebral blood flow in normal aging (Madden & Hoffman, 1997). Although the aging brain may have a capacity for compensatory redistribution of reduced blood flow in response to cognitive challenge (Jennings et al., 1998), with impaired vasoregulation, such compensation may be insufficient. This unfavorable state of affairs may be negatively modulated by such life-long risk factors as social stress, which by itself exacerbates cerebral ischemia (Sugo et al., 2002). Thus, the prefrontal regions may be the least capable of accommodating fluctuations in perfusion that accompany the hypertensive condition (especially in older adults) and may be the most vulnerable to the cumulative pathogenic effects.

Methodological Limitations of the Study

An obvious limitation of this study is limited statistical power. Would it be possible that in a larger sample the null hypotheses (lack of differences) could have been rejected? Examination of most of the observed effects suggests that if the magnitude of the effects present in this sample were preserved, rejection of the null hypothesis would be unlikely, as most of the nonsignificant group effects were too small, and with $F < 1$, could not be significant

with any number of subjects. The only effects that could have reached the conventional level of significance were the differences in fluid reasoning ($F = 1.77$, which corresponds to $d = .29$ or $r = .15$) and vocabulary ($F = 2.78$, $d = .37$, $r = .18$) scores. Such effects are considered small (Cohen, 1977) but they could have attained significance in samples of 121 and 84 subjects, respectively.

Because actual blood pressure measures were available only for a part of this sample, we cannot be certain how many of the nominally normotensive participants actually were normotensive, and how successful was the antihypertensive treatment. If approximately 27% of ostensibly healthy adults are unaware of their incipient hypertension (Burt, Cutler, et al., 1995), then up to 11 of the controls could have actually had elevated blood pressure. Three factors make that an unlikely proposition. First, the available blood pressure data indicate that, on average, the controls were normotensive. Second, the population figure of 27% unaware hypertensives may not apply to a sample of healthy adults with college education and unimpeded access to health care. In all likelihood, the rate of persons with hypertension in the control group was much lower. In any case, overlap between the groups would have increased the likelihood of negative results, rather than producing spurious findings. Third, a conservative definition of hypertension used by most physicians who treated the patients in this study might have resulted in misclassification of the subjects. It is possible that some participants with systolic blood pressure of 130–135 mm Hg and diastolic blood pressure of 80–85 mm Hg—levels usually considered only somewhat elevated—harbored significant risks for cardiovascular disease and cerebrovascular deterioration (Panza, 2001). Such mild elevations could have resulted in elevated WMH burden and local brain matter shrinkage in the nominally normotensive participants. Thus, the deficits observed in this study may represent the best-case scenario, with the actual differences being even larger. Among 20 nominally normotensive participants who had actual blood pressure measures, only 1 exhibited readings consistent with Stage 2 hypertension. Reanalyses conducted on a subsample of people who had measured blood pressure suggests that, by and large, the effects are robust and are not influenced by possible incorrect diagnostic classification. Although some of the differential effects of hypertension on cerebral regions cannot withstand such a drastic reduction in statistical power (e.g., elimination of the differences in the prefrontal white matter volume), the majority (differential reduction of prefrontal cortical volume, increase in prefrontal WMH, and increase in perseveration) remained intact.

The participants of this study were hardly typical geriatric patients with hypertension. A survey of current literature indicates that even when the goal of treatment is to reduce systolic blood pressure to a borderline high level (150 mm Hg), drug therapy yields only a 60–70% success rate (Prisant & Moser, 2000). Thus, interpolating from the subsample of participants for whom blood pressure measures were available, we infer that the hypertensive group in this study can be characterized as successfully treated. In addition, the participants in this study were free from diseases and adverse conditions that are frequently associated with hypertension, such as diabetes, renal and hepatic failure, congestive heart failure, and stroke. This line of reasoning buttresses the argument that this was a very healthy group of middle-aged and older adults,

and the results of the study represent an attenuated picture of the effects of hypertension on brain and cognition.

Regional brain volumes and the volumes of WMH were computed from images acquired with different in-plane resolution and slice thickness; they were not coregistered. Thus, the volume of WMH was not excluded from the regional white matter volumes. As a result, the prefrontal and parietal white matter volumes included “dead weight” of the WMH, and therefore overestimate the true functional volumes of those regions. It is interesting that the correlation between PFC white matter and frontal WMH volumes was $-.37, p < .05$ (i.e., people with smaller volumes of PFC white matter actually had larger burden of frontal WMH). Thus, inclusion of WMH made the test of the hypothesis more conservative.

Having only one measure of executive functions is another limitation of this study. Future studies should involve at least two measures of each construct to ensure its validity. On the other hand, some other cognitive indices used in this study (working memory span measures, matrix reasoning subtests of the CFIT) are related to multiple executive functions, yet they showed no hypertension-related differences. Because perseverative errors were residualized on total errors, the performance decrement shown by hypertensive individuals is unlikely to be an expression of nonspecific factors associated with the disease or its treatment. Thus, the cognitive deficit associated with history of hypertension appears quite specific and circumscribed.

The study reported here was driven by a specific set of hypotheses based on the current accounts of neural and cognitive effects of hypertension. These hypotheses and a comparatively small sample size dictated the selection of a relatively limited scope of anatomical and cognitive measures. Thus, there is no assurance that no additional significant differences would be observed in either domain if more cerebral regions and more cognitive abilities were measured. Although true on its face value, such a critique would have to account for the fact that a broad range of regions, from prefrontal to pericalcarine, and a broad range of cognitive abilities were sampled in this study, with no positive findings obtained. Using a multitude of measures in the framework of a hypothesis-free approach on a sample of 80 would have resulted in capitalization on chance. However, in future studies, the addition of at least two cognitive domains known to be affected by age and hypertension—delayed episodic recall and perceptual–motor speed—may be informative.

Conclusions and Implications

What are the implications of the presented findings for treatment of hypertension? Not surprisingly, the earlier, the better. The “bad news” of selective vulnerability of executive functions to hypertension and aging only reinforces the “good news” of their selective sensitivity to the beneficial effects of aerobic training (Hall, Smith, & Keele, 2001; Kramer et al., 1999; van Boxtel, Paas, et al., 1997). Moreover, improved aerobic fitness, which is effective in combating hypertension (Lesniak & Dubbert, 2001), is associated with alleviation of age-related differences in brain structure, especially in the PFC and prefrontal white matter (Colcombe et al., 2003). The corollary of the latter is that attention to maintenance of normal blood pressure holds a promise of neuroprotection for older adults. The question remains whether a combination of

medical treatment and improved fitness may pave the road to complete alleviation or prevention of the cerebral and cognitive effects of high blood pressure.

More than half a century ago, Apter and colleagues (Apter, Halstead, & Heimburger, 1951) observed that “impairment of cerebral functions equivalent to that seen in patients with surgical removal of both frontal lobes may occur early in the course of essential hypertension” (p. 812). The results reported here suggest that although this statement is exaggerated in its assessment of the magnitude of the effect, it points in the right direction. The results of our study also reinforce the admonition to pay close attention to hypertension as a confounding factor in studies on aging and cognition (P. K. Elias et al., 1995), at least when executive functions are concerned.

Finally, the results of this study may have an important implication for the understanding of patient compliance and management of hypertension treatment. The latter requires a substantial amount of planning and self-management in a complex context of adherence to medical treatment, diet, and exercise. Thus, one may speculate that people who suffer from hypertension may be at risk of making decisions that exacerbate the very deficits that adversely affect the decision processes. It may be worthwhile to examine the specifics of the decision-making process in hypertension and its effects on compliance and treatment efficacy.

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Received February 5, 2003

Revision received June 9, 2003

Accepted June 17, 2003 ■