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ORIGINAL ARTICLE

Regional grey matter shrinks in hypertensive individuals despite successful lowering of blood pressure

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The aim of the study was to determine whether the reduction in brain grey matter volume associated with hypertension persisted or was remediated among hypertensive patients newly treated over the course of a year. A total of 41 hypertensive patients were assessed over the course of a 1-year successful anti-hypertensive treatment. Brain areas identified previously in cross-sectional studies differing in volume between hypertensive and normotensive individuals were examined with a semi-automated measurement technique (automated labelling pathway). Volumes of grey matter regions were computed at baseline after a year of treatment and compared with archival data from normotensive individuals. Reductions in regional grey matter volume over the follow-up period were observed despite successful treatment of blood pressure (BP). The comparison group of older, but normotensive, individuals showed no significant changes over a year in the regions tested in the treated hypertensive group. These novel results suggest that essential hypertension is associated with regional grey matter shrinkage, and successful reduction of BP may not completely counter that trend.

Introduction

Multiple *in vivo* and postmortem studies of brain morphology demonstrate that hypertensive individuals show greater loss of tissue than age-matched control individuals.[1] Hypertension, even at mild levels, acts as a negative modifier of aging as it enhances morphological alterations in brain indices typically associated with advanced age. Such effects include expansion of ventricular and sulcal spaces, decreased total and regional grey matter volume, increased burden of white matter abnormalities (for example, white matter hyperintensities) and deterioration of the micro-structural organization of the white matter.[2–7] Although differences in imaging technology, nomenclature, analytic approach and areas examined across studies impede generalizations, existing literature suggests in addition that the negative effects of hypertension on the brain involve structures that are relatively age invariant. Across studies, several regions emerge as especially vulnerable to negative modification by essential hypertension. These include prefrontal cortex,[6,8,9] hippocampus,[6,10,11] the inferior temporal cortex[7,12] and inferior parietal lobule.[13] Hypertension also affects brain regions that are only moderately vulnerable to aging, for example, supplementary motor areas,[8,14] cuneus,[12] thalamus[15] and entorhinal cortex.[13] Some studies show that regions that are usually resistant to aging, such as the primary visual cortex, shrink in hypertensive individuals.[7] The effects of hypertension may differ between the sexes. Some studies find the vulnerability only in men,[8,12,14] whereas others report such effects only in women,[12] with some (albeit not consistent) indication of lateralization.

The role of various anti-hypertensive medications in the modifying effect of hypertension is unclear, as participants have been typically studied while medicated, although some samples were comprised of never-medicated patients[8] or patients who discontinued medication before testing.[15] Notably, most extant studies of hypertension and brain morphology were cross-sectional, and the longitudinal

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studies[13] included too few hypertensives to afford a sufficient statistical power for discovering relatively subtle effects. In light of the discussed inconsistency of the literature and the confounding of diagnosed hypertension with medication, we designed this longitudinal study. In a 1-year follow-up, we examined the impact of pre-existing untreated hypertension and the potentially curative influence of its alleviation on the regional brain shrinkage.

In addition to changes in brain structure, we examined the impact of hypertension and anti-hypertensive treatment on neuropsychological measures. Although both aging and hypertension are associated with declines in cognitive performance,[16] the literature concerned with specific associations between structural change and cognitive function is inconsistent.[1,8,15,17]

The current longitudinal investigation focused on 1-year changes in brain morphology among persons who received a diagnosis of hypertension and were treated with medication to lower their blood pressure (BP). If heightened BP proximally induces morphological changes in the brain, it is plausible that reducing BP may normalize brain morphology. Even if such intervention would not reverse the damage, it could at least attenuate further structural deterioration. Hence, we compared the effect of two medications that have been proven effective in reducing BP in uncomplicated hypertension: a β-blocker and an angiotensin-converting enzyme inhibitor. Although both interventions were expected to reduce BP, the angiotensin-converting enzyme inhibitor was expected to have a more favourable neuroprotective effect given its reported action of normalizing the vascular wall.[18,19] To assess brain morphology, we used techniques designed to extend methods employed in previous studies by using full-brain coverage, an automated identification of specific brain regions, and a focused statistical approach. We used a previously validated and widely used automated labelling procedure (ALP). In this approach, after segmentation into grey matter, white matter and cerebrospinal fluid (CSF) compartments, the algorithm identifies, labels and quantifies the volume of 194 areas based on whole-brain, structural magnetic resonance images.[20,21] We selected brain regions of interest (ROIs) according to the extant reports identifying them as discriminating between hypertensive and normotensive individuals, as discussed above. A comparison group consisted of healthy normotensive individuals with magnetic resonance imaging (MRI) scans acquired on two occasions separated by 1 year; those data were available from the public dataset of the Alzheimer's Disease Neuroimaging Initiative (ADNI) Study.

Methods

Participants

Hypertensive participants were community volunteers recruited from a major metropolitan area in the United States of America. They were between 35 and 65 years of age, and had arterial BP in excess of the cutoff established by the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure:[22] an average diastolic fifth-phase BP of 90 mm Hg, systolic BP of 140 mm Hg or both. For safety reasons, volunteers were referred for separate clinical treatment rather than accepted in the study if diastolic pressure was above 109 mm Hg or systolic pressure above 179 mm Hg. BP measures (auscultatory technique with a mercury manometer) were taken with a participant sitting after at least a 5-min rest. Baseline BP was calculated from the average of the last two of three readings performed on two occasions. Participants were required to have either no previous pharmacological treatment for hypertension or no more than 6 months of BP medication within the past 5 years, with no BP medication taken in the 6 months preceding enrolment. For detailed inclusion/exclusion criteria for this study, see an earlier publication.[23] Screening was designed to exclude secondary hypertension, use of drugs/substances interfering with accurate and safe treatment/assessment and presence of other serious disease, notably coronary or cerebrovascular disease. Of the 81 volunteer patients, 36 did not meet the inclusion criteria and of the remaining 45, 41 completed the entire study and 40 had a full set of structural MRI and neuropsychological measures. Among participants analyzed for either MRI or neuropsychological results, 27 entered the study with both systolic and diastolic pressure elevated, 9 with systolic elevated only and 6 with diastolic elevated only. Participants were not selected for handedness or race; 95% of completing individuals reported being right-handed and 85% were Caucasian. Participants were similar to non-completing individuals in age, education and personality factors. However, continuing participants were significantly (χ^2-test, $P<0.05$) more likely to be male, Caucasian and married. The University of Pittsburgh Institutional Review Board approved all procedures as consistent with ethical principles and subjects provided informed consent.

The imaging data for a comparison group of normotensive participants were obtained from a public database compiled by the ADNI (http://www.loni.ucla.edu/ADNI). The ADNI was launched in 2003 as a collaboratively funded public/private effort directed over a period of 5 years to test whether serial MRI, positron emission tomography, other biological markers and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment and early Alzheimer's disease. Appropriate structural MR samples separated by 1 year from normotensive individuals were selected. We identified such data using the control volunteers from the ADNI dataset. ADNI controls were defined by reported good health, below cutoff BP and absence of anti-hypertensive

medication. These images were acquired from several different sites using 1.5T Siemens (New York, NY, USA) and GE scanners (Milwaukee, WI, USA), in accordance with the published ADNI protocol.[24] The ADNI protocol uses a similar volumetric spoiled gradient-recalled sequence to that used in our study. Age and gender were considered in selecting individuals for use, but exact matching was not possible. All the members of the comparison group were of Caucasian race. This normotensive data set was segmented and analyzed with ALP using the procedures described below. Procedures and testing described below only are applicable to hypertensive participants.

Design

Hypertensive participants were tested in three to four sessions, which included BP assessment, medical screening and history, physical examination, administration of self-report questionnaires, neuropsychological examination, MRI and functional positron emission tomography examinations.[23] Briefly, the functional scans included rest and checkerboard scans, as well as a sequence of scans assessing working memory, see ref. 23. All examinations were repeated after 1 year, except for the screening and self-report instruments. Owing to its representativeness of other BP measures, its utility in epidemiological work and our need to control number of analyses performed, systolic BP was used in all analyses.

Medication procedures

Patients were treated for 1 year within a randomized double-blind design. Two medications were administered: lisinopril (the angiotensin-converting enzyme inhibitor) or atenolol (the β-blocker). The choice of drugs was based on the initial hypothesis that lisinopril would alter brain function more than atenolol.[25] The dose was adjusted in a 6-week titration phase of the study to achieve a BP of <140/90 mm Hg. The dose of hydrochlorothiazide was added to achieve BP control in 11 of the patients who had an insufficient BP response to their assigned treatment. Details of dosing and other procedures including functional positron emission tomography results are available elsewhere.[25]

Structural MRI measures

All subjects underwent a structural MRI on a GE Signa 1.5T scanner to provide a detailed image for current morphometry as well as mapping positron emission tomography results. A brief scout T1-weighted image was followed by an axial series oriented to the plane along anterior and posterior commissures: fast spin-echo T2-weighted, proton density-weighted and fast fluid-attenuated inversion recovery.[26] A field of view of 24 cm and image matrix of 256×192 pixels were used for all axial MR series. A volumetric spoiled gradient-recalled sequence with parameters optimized for maximal contrast among grey matter, white matter and spinal fluid was acquired in the coronal plane (TE/TR = 5/25 ms, flip angle 40°, one excitation, slice thickness 1.5 mm and no gap) for purposes of the current analyses. This report focuses on brain morphology measures from the spoiled gradient-recalled images. Severity of white matter hyperintensities, ventricle size and sulcal size were judged from the axial scans, and the relationship of these to hypertension treatment has been previously reported.[27] Participants showing evidence of significant lacunar or other infarcts identified from the MRI films by a board-certified neuro-radiologist ($n = 2$) were excluded before treatment for hypertension. Significant infarcts were those that were judged to potentially influence functional images and/or influence cognitive processing.

To determine volumes of grey and white matter and CSF, we employed a procedure referred to as the ALP. We have applied this in previous structural MRI studies to automatically label-specific anatomic regions, for example,[28–35] ALP is used to register the colin27 template brain[36] to a three-dimensional T1-weighted high-resolution image of each subject. Before the registration, the skull and scalp are stripped from both colin27 and the subject's three-dimensional T1-weighted image using the brain extraction tool,[30] and followed by semi-automated erosion and dilation to remove additional skull and scalp.[35] We use a fully deformable registration model similar to that described by Chen[37] and implemented the procedure using the registration library in Insight Segmentation and Registration Toolkit (ITK).[38] This method starts with a grid-based piecewise linear registration and then uses the Demon's registration algorithm[32] as a fine-tuning procedure for a voxel-level spatial deformation. The fully deformable registration allows for a high degree of spatial deformation, which seems to give it a particular advantage over other standard registration packages, such as AIR and SPM.[34] After registration of the template to the individual subject space, the ROIs from the template are applied to label regions on the subject's MRI, that is, volumes are estimated in the participant's 'native space'. The number of grey, white and CSF voxels in each of these regions are then counted to produce a table of ROI volumes for each region and each subject. The anatomic ROIs are from a previously published atlas (90 manually traced regions),[33] the Brodmann atlas (82 regions, included with the MRIcro software package)[29] and from locally generated regions defined from manual tracing.[34] Figure 1 illustrates the delineation by ALP of the grey matter volume of a particular area, the hippocampus, in one participant.

Regions selected for hypothesis testing were areas showing statistically significant differences between hypertensive and control individuals in the studies reviewed in the previous section. We examined the nine ROIs, defined bilaterally, using Brodmann area (BA) nomenclature for cortical areas. These choices
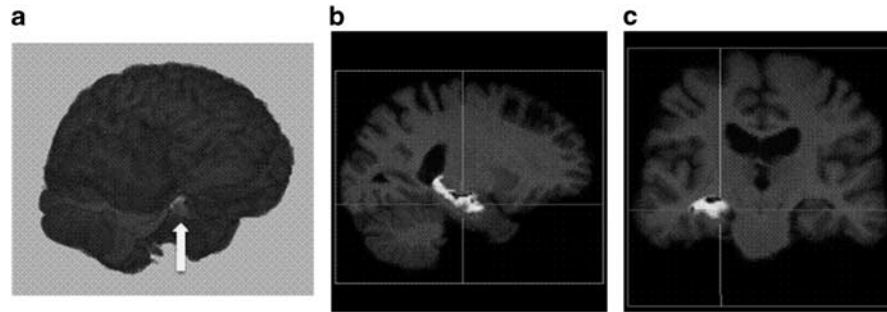
Figure 1 Left hippocampal segmentation with ALP from one subject in the sample. (**a**) Three-dimensional surface rendering with left hippocampal segmentation identified by arrow, (**b**) sagittal view and (**c**) coronal view.

Table 1 Brain regions of interest examined based on prior cross-sectional reports

Region of interest	BA	Lobe
Supplementary motor area	BA6	Frontal
Medial frontal	BA8	Frontal
Superior prefrontal	BA9	Frontal
Cuneus	BA18/19	Occipital
Mid temporal	BA21	Temporal
Entorhinal cortex	BA28	Temporal
Inferior parietal	BA39	Parietal
Hippocampus	—	Subcortical
Thalamus	—	Subcortical

Abbreviation: BA, Brodmann area.

were made to reduce the probability of spurious results, that is, control experiment-wise error and to provide a specific terminology for the areas examined. Note that previous studies did not employ common nomenclatures or similar degrees of specificity in their labelling of regions; thus, it was impossible to derive ROIs with specific spatial coordinates from the descriptions provided in these studies. Table 1 lists the ROIs examined. We further correlated grey matter regions and systolic BP between the current control sample and the pre-treatment hypertensive sample. In exploratory analyses, areas that showed a significant correlation were also tested for change across the year of treatment for the hypertensives and the comparable year for the controls.

Neuropsychological assessment
Cognitive functioning was assessed with a 2-h battery of well-known neuropsychological tests used routinely in clinical practice. The battery-emphasized tests of memory and executive functions were previously shown to be influenced by hypertension.[16] Tests include an estimate of intelligence (National Adult Reading Test revised for US samples),[39] verbal learning and memory (Rey Auditory Verbal Learning Test and Newspaper Story Test, incidental memory after the Digit Symbol Substitution Test),[40,41] non-verbal learning and memory (Rey

Complex Figure and Wechsler Faces), semantic memory (Verbal fluency[42] and Boston Naming Test),[43] working memory (Four-Word Working Memory,[44] Wechsler Memory Scale 3 Letter Number Sequencing and Spatial Span), psychomotor efficiency (Grooved Pegboard),[45] attention/mental flexibility (Trail Making,[46] WAIS Digit Symbol Substitution and Stroop Color/Word Interference[47]).

To limit the number of comparisons, we reduced pre-treatment neuropsychological data to four factors via a principal component analysis with varimax rotation. The factors were labelled: Verbal Memory (Logical Memory, first recall; Auditory Immediate Memory, Auditory Delayed Memory; Four-Word Short-Term Memory; and Verbal-Paired Associates), Visuospatial Memory (Family Pictures immediate and delayed, Visual Immediate Memory and delayed, and General Memory Index), Psychomotor Speed (Grooved Pegboard preferred and non-preferred hands) and Spatial Construction (Object Assembly and Block Design). Working memory performance on the n-back tasks tested both in the scanner and in the neuropsychological testing was also examined. Working memory was assessed using a non-parametric A' sensitivity index derived from the proportion of hit and false alarms observed in the responses of the subjects.[48,49]

Analysis
Volumes of the target ROIs served as dependent variables in a general linear model that also contained pre–post 1 year as a repeated measure factors, gender and hypertensive versus control as grouping factors and age and intra-cranial volume (average of pre and post estimates) as continuous independent variables. Age has known effects and the intra-cranial volume adjusted for individual differences in head/brain size. The ROIs served as a multivariate-dependent variable, with significant effects then assessed with univariate follow-up tests. Multivariate analysis with a type III decomposition was applied to estimate well-interaction effects of primary interest and account for dependency in the assessment occasions.[50] Analyses were also performed separately within the hypertensive and

normotensive groups to confirm results from the multivariate analyses as it was possible that covariance in the presence of group differences might violate assumption of covariance analysis.[51] The sample size did not permit adding all possible covariates simultaneously, but a number of potentially important covariates were added individually to ensure that they were not major confounders of the results. These were body mass index, initial BP, educational level, and for hypertensive analyses, type of medication and BP response to mediation. Areas previously implicated in longitudinal studies of brain aging were also examined to see whether comparable change hypertensive and control individuals occurred in these areas over the 1-year period.[17] Following these analyses, correlations were computed between pre-treatment systolic BP in the patients and initial systolic BP in the controls and bilateral regional grey matter estimates. Areas showing significant correlations were then tested in an exploratory linear model identical to the one performed for the pre-planned ROI analysis. We used a different approach with the white matter and CSF volumes as we lacked any previous results from these subjects to guide the analyses. We tested the difference over a year in total brain white matter and CSF. Any trend could then be followed up by regional testing.

Results

Table 2 shows the characteristics of the hypertensive and normotensive samples. The normotensive sample was small because of the limited number of individuals with 1-year test/retest in the ADNI database that were normotensive and demographically and physically comparable to the hypertensive samples. As shown in the table, neither age nor body weight was strictly comparable between the samples. The table presents characteristics of our sample taken as a whole because atenolol and lisinopril had comparable effects on BP in the two treated

hypertensive groups—a decrease of ~ 22 mm Hg systolic and 18 mm Hg diastolic. Table 3 illustrates further the overall success of the pharmacological treatment. Although some variability in response to medication is evident, titration was largely successful by week 6 in reaching normotensive levels in the majority of the patients, and further BP reduction is evident through week 38. Further description of the hypertensive sample and treatment is available.[23,27] Although uniformly tested in our statistical models, the two medication groups yielded essentially identical results. None of the effects involving medication as a grouping factor approached significance, and therefore, medication will not be discussed further.

The primary focus of this study was on change in the regional volumes of brain volumes of the hypertensive patients over the course of treatment. These results were compared with the sample of normotensive individuals drawn from the ADNI database. The findings for the regional grey matter volumes in hypertensive individuals and normotensive comparisons are presented in Figure 2. The multivariate analysis of the pre- to post-treatment change in the hypertensive and control group, with age, gender and intra-cranial volume as covariates, showed an interaction of diagnostic group (hypertensive versus comparison group) by occasion (readings separated by a year, that is, pre- versus post-treatment in the hypertensive group; F (9,43) = 8.09, Wilks $\Lambda = 0.37$, $P < 0.001$ and partial $\eta^2 = 0.63$). Main effects were also observed for diagnostic group (F(9,43) = 2.60, Wilks $\Lambda = 0.65$, $P < 0.02$ and partial $\eta^2 = 0.35$), measurement occasion (F(9,43) = 2.48,

Table 3 Percentage of patients failing to meet normotensive levels of systolic and diastolic pressure by week of clinical visit

Week	4	6	23	38
Systolic pressure > 140 mm Hg (%)	9.3	6.9	3.7	3.1
Diastolic pressure > 90 mm Hg (%)	5.6	5.6	3.1	2.5

Table 2 Demographic characteristics of the hypertensive and normotensive samples

Variable	Hypertensive (n = 41)	Normotensive (n = 16)	t-test	P-value
Age (years)	52.4 (7.1)	65.9 (3.9)	−7.2	< 0.001
Gender (% female)	24	38	$\chi^2 = 0.9$	NS
Height (cm)	173.5 (7.4)	169.9 (8.4)	1.6	NS
Weight (kg)	88.9 (15.4)	77.1 (17.7)	2.6	< 0.02
BMI	29.6 (4.8)	26.5 (4.9)	2.2	< 0.04
Systolic BP(mm Hg)	148 (11)	126 (8)	7.2	< 0.001
Diastolic BP(mm Hg)	95 (8)	75 (7)	8.4	< 0.001
Education (years)	15 (2)	16 (3)	−1.1	NS
Whole-brain grey (mm³)—pre	625.8 (75.7)	635.0 (68.9)	−0.4	NS
Whole-brain Grey (mm³)—post	612.8 (79.9)	627.5 (66.1)	−0.6	NS

Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; BMI, body mass index; BP, blood pressure; NS, not significant.
Figures in parentheses in body of table are standard deviations. The *t*-values compare hypertensive and normotensive groups; χ^2-test is used to compare gender composition of the groups. Pre–post changes in whole-brain grey are not significant overall or within each group. Note that because of sample size differences and possible method variance, the standard error of the mean was larger in the ADNI control sample (s.e. = 17) than in the hypertensive sample (s.e. = 12).
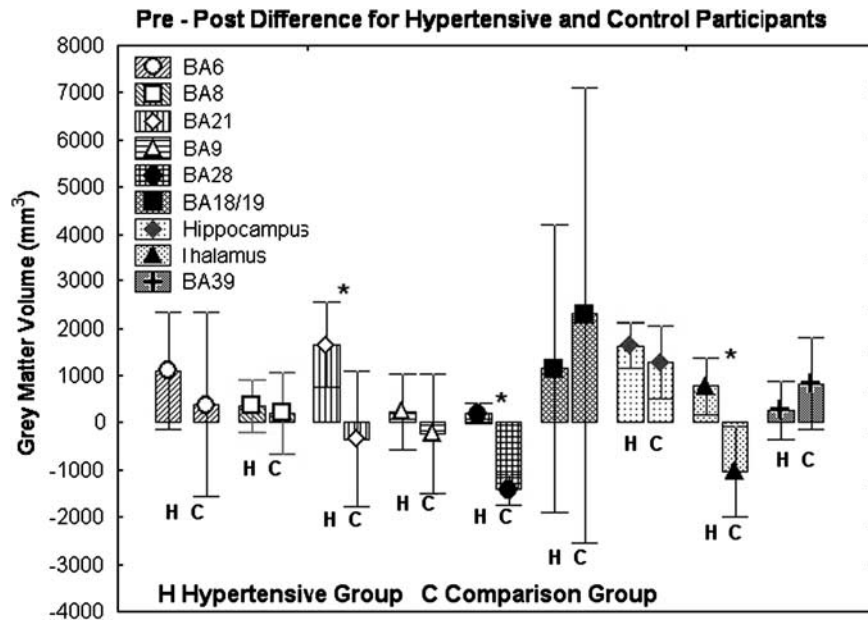
Pre - Post Difference for Hypertensive and Control Participants

Figure 2 Pre- minus post-year differences in grey matter volume in cubic millimetres among treated hypertensive individuals (H) and normotensive comparison individuals (N). Differences are presented separately for brain areas as classified within ALP (see text) that showed changes over the 1-year period. Error bars reflect the 95% confidence intervals. Positive differences show shrinkage over the course of a year. For each area, left bar is change among hypertensive (H) individuals and right bar normotensive individuals (N). Figure illustrates significant statistical interaction between pre versus post and hypertension versus control. Comparisons indicated with * are significant in comparison of individual areas.
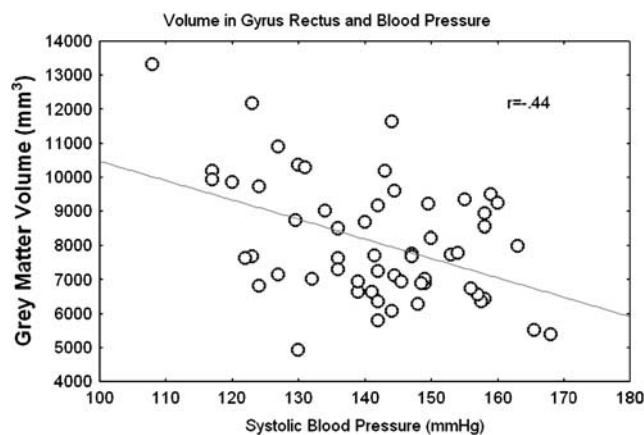

Figure 3 Correlation between grey matter volume in the gyrus rectus and systolic BP for the entire sample using the pretreatment BP of the patients and the BP at initial scan for the controls.

Wilks $\Lambda = 0.66$ and partial $\eta^2 = 0.34$) and intra-cranial volume (F(9,43) = 8.64, Wilks $\Lambda = 0.36$, $P < 0.001$ and partial $\eta^2 = 0.64$). Other interactions involving the diagnostic grouping were not significant. The follow-up of univariate tests showed significant group × occasion interactions for BA21 (F(1,51) = 4.44, $P < 0.05$ and partial $\eta^2 = 0.08$), BA28 (F(1,51) = 55.54, $P < 0.001$ and partial $\eta^2 = 0.52$) and the thalamus (F(1,51) = 8.10, $P < 0.01$ and partial $\eta^2 = 0.14$).

Despite the loss of statistical power, separate multivariate analyses of the groups yielded useful

information. Analysis of the hypertensive group showed a significant interaction between gender and treatment: F(9,29) = 4.10, Wilks $\Lambda = 0.44$, $P < 0.002$ and partial $\eta^2 = 0.56$. Follow-up univariate analyses revealed that primary sources of the interaction were women showing greater grey matter loss in BA21 and the hippocampus relative to males. The means (standard error) relevant to this interaction were as follows. For BA21: males baseline volume = 26 040 (s.d. = 520) mm³ and follow-up volume = 25 947 (527) mm³; for the females, baseline volume = 27 228 (970) mm³ and follow-up volume = 24 885 (982) mm³. For the hippocampus, the volumes were as follows: males, baseline volume = 12 261 (266) mm³ and follow-up volume = 11 530 (182) mm³; for the females, pre = 14 221 (340) mm³ and post = 11 502 (497) mm³. No significant effects were observed in the analysis of the comparison group.

Following the analyses of areas derived from the literature, we conducted an exploratory correlational analysis of the baseline systolic BP and bilateral grey matter volumes. The analysis yielded significant correlations ($P < 0.02$ or better) for superior orbital frontal cortex, lateral orbital cortex, gyrus rectus, cerebellum and BA11. Figure 3 illustrates these findings by showing the scatter plot for the relation of the gyrus rectus grey matter volume and untreated systolic BP. Grey matter shrinkage over a year was then assessed for areas that showed correlation with systolic BP but had not been previously tested in a 1-year longitudinal analyses. The only regional difference that emerged from this

analysis was a pre–post difference in the gyrus rectus grey matter (F(1,51) = 6.22 and P < 0.03). The means (standard error) constituting this interaction were as follows: for the hypertensive participants, pre = 12 358 (361) mm³ and post = 7 718 (303) mm³ and for the normotensive sample, pre = 12 789 (570) mm³ and post = 9 637 (479) mm³.

Correlations with cognitive performance scores were minimal. Correlations were computed for the areas showing change over the treatment period. Change in these areas was compared with change in the neuropsychological factor scores as well as the 2-back memory performance accuracy during the scanning. Correlations with the neuropsychological factors were not significant; none of the neuropsychological factors were even minimally correlated with the change in grey matter volumes in the tested areas.

Another set of analyses focused on aging effects to examine whether areas known to change with aging were showing similar changes in hypertensive and control participants. We examined the regions that were identified as vulnerable to aging in a recent review of the literature.[17] These were temporal and frontal cortices, hippocampus, entorhinal, cortex, caudate nucleus and cerebellum. These analyses typically showed statistically marginal decreases in area volume over the year, with essentially equivalent changes between normotensive and hypertensive individuals. The exception was the temporal lobe that showed a significant decrease in cortical volume across the year (F(1,55) = 5.3, P < 0.03, 11 088 (647) to 10 333 (687) mm³. The entire temporal lobe within each group evidenced significant shrinkage within the hypertensive group (F(1,54) = 5.8, P < 0.03, see mid temporal and entorhinal results above as well) but only marginal change in the control group:(F(1,13) = 3.6 and P = 0.08.

We found no change in CSF and white matter volume over a 1-year period in either hypertensive or control participants. Post–pre comparisons were uniformly nonsignificant (P > 0.3); hence, further regional comparisons are not reported.

Discussion

The central finding in this study is that alleviation of hypertension and reduction of BP to normotensive levels failed to prevent grey matter loss over 1 year of treatment. As noted previously, grey matter morphology differences related to hypertension appear to differ from those related to normal aging, for example, see refs 7,9,17. It is possible that high BP induces central hemodynamic effects, contributing to atrophy of particular grey matter areas. On the basis of this inference, we expected that reducing BP over the course of a year might arrest or even diminish grey matter loss. Our findings suggest, however, that some aspect of essential hypertension is continuing to influence brain morphology

independently of the level of peripheral BP. Of note, another index of brain morphology, cortical thickness, was recently observed to correlate negatively with BP in pre-hypertensive individuals.[52] More generally, a recent review of structural neuroimaging studies of the aging brain[53] concluded that treatment of hypertension reduces, but does not eliminate, effects of aging on the brain. As summarized in that review, compared with normotensives, treated hypertensives have more white matter hyperintensities, prefrontal volume shrinkage and reduced hippocampal volume.[11,54–56]

We must emphasize the fact that we only studied two medications over a year of treatment. The literature is not specific enough to determine whether areas specifically related to hypertension show continued or arrested atrophy with longer-term treatment. It is possible that early intervention as well as longer duration of intervention would maintain grey matter morphology among treated hypertensive individuals. Alternately, it is conceivable that medication rather than a hypertensive process affects grey matter morphology. We cannot discount this possibility without a placebo control arm to our study, but doubt on this hypothesis is cast by our finding that two medication groups did not differ in their morphology changes despite differences in the mechanism of action of the two medications.

We observed volume loss in nine brain regions over the course of a year of treatment lowering BP. The grey matter regions were chosen for this study specifically because of previous cross-sectional findings of their smaller volume in these areas in hypertensive individuals compared with normotensive controls. Shrinkage of specific grey matter regions after a year of effective anti-hypertensive treatment is in accord with the cross-sectional findings in similar brain areas. The validity of our results rests primarily on this longitudinal verification of cross-sectional results. In the hypertensive group, in seven of the nine examined regions, we observed a mean 1-year loss that exceeded shrinkage in the normotensive sample.

Caution is required in interpreting the statistical inferences given the variability of the results in the small comparison sample. A portion of the variability may be due to the use of different scanners at different sites in the comparison sample drawn from the ADNI Study. Despite this variability, the utility of the comparison sample was supported by the typical age-related changes in grey matter volume observed. Changes over a year in the percentage of grey matter relative to intra-cranial volume were similar to those reported in the literature. These changes were the same in women as estimates obtained in large samples by Taki[57] and slightly higher, but well within the range of values for men. Importantly, the results do not depend entirely on the comparison sample, as the larger hypertensive sample showed decreases in grey matter volume

across all of the nine areas examined, albeit varying in degree of decrease. Exploratory analyses suggested that longitudinal changes in treated hypertensives was largely confined to the areas defined *a priori*, although gyrus rectus was identified as decreasing more in hypertensives relative to controls in these exploratory analyses. The gyrus rectus has not been well studied specifically in hypertensives, but its grey matter has been shown to decrease with age[58] and to correlate with diagnosis of unipolar depression,[59] age-related differences in the olfaction[60] and performance on executive function tasks.[61]

Although some of the examined regions were identified in previous work as hemisphere or gender specific, our conservative strategy was to test areas bilaterally and across genders in an attempt to avoid spurious findings. Despite this, we did find accentuated grey matter loss among hypertensives in BA21, BA28 and thalamus extending previous findings.[8,9,12,13] Follow-up analyses showed that the loss in BA21 was greater in women than in men. Medial frontal and hippocampal areas showed directional effects, but were not separately significant discriminators between hypertensives and controls,[6,10–12,14,17] although our follow-up analysis showed hypertensive women showing hippocampal loss that was greater than that among men. Occipital and inferior parietal areas showed no losses among hypertensives relative to controls over the year, despite some evidence of such loss longitudinally in occipital cortex[7] and cross-sectionally in inferior parietal cortex.[13] We have no explanation for this. Aging has typically been shown to influence the occipital areas less than the other areas we examined, although the parietal lobe is typically shown to be influenced by age.[62–64] An increase in cerebellar CSF with hypertension was previously reported by Strassburger *et al.*,[15] but we did not replicate this finding and found no substantial differences in white matter or CSF volumes over the year of treatment. As noted earlier, functional correlations of grey matter change have not been widely investigated. We examined this question but found no strong correlations between neuropsychological function and the decrease in grey matter volume over a year. Neuropsychological deficits related to hypertension are small, and the current sample size as well as the relatively short (1 year) time frame may have obscured any ongoing functional changes related to grey matter volume loss.

These analyses driven by previous literature were supplemented by a *post hoc* examination of BP and grey matter volume in the current sample. Using pre-treatment and control participant BP, we found relations between systolic BP and superior orbital frontal cortex, lateral orbital cortex, gyrus rectus, cerebellum and BA11. Note that areas detected did not include all the areas assessed in our longitudinal analysis; more information is clearly needed on the time course of morphological changes. Slow, incremental change would not have been detected in our 1-year study. We did not detect interactions with age or gender (overall), but it is possible that morphological changes are accentuated in older sample or cluster around menopausal periods in women.

Mechanisms accounting for the precise pattern of grey matter change in hypertension are unclear. General changes in brain morphology have been related to small-vessel arteriosclerosis and lipohyalinosis, as well as rarefaction, white matter lesions, oxidative stress, neuronal shrinkage, apoptosis, local ischaemia and β-amyloid deposition.[65–68] It remains unclear how hypertension accelerates these factors, as these reviews indicate, and it is equally unclear at present why these mechanisms would be specifically active in the regions identified in our study. Areas showing specific loss with hypertension were subsumed within larger regions typically associated with aging, for example, temporal lobe. Our analyses directed at areas known to show changes with aging suggested accelerated aging in the temporal lobe of hypertensives, although other areas seemed to show equivalent aging effects between hypertensive and control participants. Given this, we cannot determine at this point whether hypertension accelerates processes related to normal aging in specific areas or introduces new factors independently of normal aging process. Overall, temporal and thalamic changes appeared the most robust in the current sample. Future work with fine-grained analyses will be required to clarify the possible mechanisms.

Our study has several limitations. The most prominent is that we were unable to find closer matching between the groups. The members of a small sample obtained form LONI ADNI database differed from our hypertensive participants in age and body mass index. This comparison provides only initial data, suggesting the observed losses in the hypertensive patients were not due to normal aging. This limitation is emphasized by the gains in grey matter volume over a year apparent in the mean data from the small comparison group; such an effect is possible, but larger sample sizes would be required to decrease the likelihood of variation due to statistical and methodological 'noise'. The ADNI sample did, however, appear to represent normal aging appropriately. Moreover, because hypertensive group was younger, there was an *a priori* lesser likelihood of finding brain shrinkage in that group rather than in older controls. This reduces a threat to validity of our conclusions. A strength of this study is that the results were not confounded by previous pharmacological treatment. However, we observed the reduction of BP with only two of the many possible medications for treating BP. Thus, generalization to patients who were exposed to various pharmacological regimens and those who were treated with different anti-hypertensive agents must be made with caution.

In summary, in cortical regions previously identified as vulnerable to hypertension, newly treated hypertensive individuals continue to show grey matter shrinkage over a year of successful treatment. The continued atrophy in the presence of successful reduction of BP suggests that essential hypertension may directly affect the brain via factors that are not mediated by increased BP. This observation contributes to accumulating research, suggesting that essential hypertension from its onset may be a disease of the brain as well as of the vasculature.[69]

What is known about this topic
- Brain grey matter volume is reduced in hypertensive relative to normortensive individuals.
- Detectible changes in degree and volume of brain blood flow activation occur among hypertensive individuals when challenged by memory tasks.
- Mild cognitive deficits are present in hypertensive individuals.

What this study adds
- Despite successful reduction of blood pressure over a year in hypertensive patients, brain grey matter continues to decrease in volume.
- Brain blood flow activation in response to memory tasks is not altered by blood pressure lowering.
- Cognitive function is not altered by blood pressure lowering over a year.

Conflict of interest

The authors declare no conflict of interest.

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