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Longitudinal changes in cortical thinning associated with hypertension

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Abstract

Background—Cross-sectional studies of the association between hypertension (HTN) and brain atrophy have shown reductions in prefrontal, temporal, and hippocampal volumes, and have identified thinner cortices across the cortical mantle.

Method—In the current study, we followed 96 participants enrolled in the Baltimore Longitudinal Study of Aging over a mean interval of 8 years (mean age at baseline = 68.7) and compared those who are hypertensive ($n = 49$) throughout the study with those who are normotensive ($n = 47$).

Results—Hypertensive individuals show an increased rate of thinning compared with normotensive individuals in several regions, including the frontomarginal gyrus in the left hemisphere, and the superior temporal, fusiform, and lateral orbitofrontal cortex in the right hemisphere. We also investigated the effects of midlife blood pressure (BP), intervisit variability in BP prior to imaging, and duration of HTN on areas that show subsequent differences in the rates of cortical thinning between groups. We found that higher midlife BP and longer durations of HTN predicted a higher rate of thinning in the right superior temporal gyrus. We also found that greater variability in SBP but not DBP predicted a higher rate of thinning in the right superior temporal gyrus, frontomarginal gyrus, and occipital pole.

Conclusion—These findings demonstrate that hypertensive individuals show increased rates of thinning compared with normotensive individuals and suggest intervisit BP variability and midlife BP contribute to these longitudinal differences.

Keywords

blood pressure variability; brain aging; cortical thickness; longitudinal change; midlife blood pressure

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Conflicts of interest

The authors declare no conflicts of interests with regard to this work.

INTRODUCTION

Vascular risk factors can serve as markers to better delineate normal from pathological brain aging. Hypertension (HTN) is associated with several brain abnormalities, including increased white matter hyperintensities [1,2], risk for dementia and Alzheimer's disease (AD) pathology [3–5], and reductions in brain volume [6–8]. A recent meta-analysis of HTN and brain atrophy concluded that while there are some inconsistencies in relating high blood pressure (BP) to brain volume, especially for cross-sectional studies, the most consistent trends are reductions in bilateral frontal gray matter and the hippocampus [9]. Additionally, cross-sectional neuroimaging studies of cortical thickness have indicated that higher BP is associated with thinner cortex [10], and have found that midlife HTN predicts thinner cortical regions later in life [11].

Although previous longitudinal studies have looked at change in brain volume over time in relation to HTN, these have been limited by short follow-ups, consisting of less than three visits per person, and were conducted on specific regions of interest (ROIs) (such as hippocampus) or total brain volume [12–14]. Thus, although cross-sectional and longitudinal analyses have discovered cortical thinning is pervasive in normal brain aging [15,16], there has yet to be a longitudinal surface-based analysis that investigates the effect of HTN on this normative aging process.

In this study, we analyzed consecutive T1-weighted MRI images for both hypertensive (HTN) and normotensive cognitively normal participants enrolled in the Baltimore Longitudinal Study of Aging (BLSA). On the basis of the previous cross-sectional and longitudinal structural imaging studies, we hypothesized HTNs would exhibit an increased rate of cortical thinning longitudinally compared with normotensive individuals. Furthermore, we expect that midlife measures collected years before their baseline MRI assessment may be predictive of these structural differences.

METHODS

Participants

All participants were enrolled in the BLSA neuroimaging substudy [17]. From this substudy consisting of 158 individuals, 121 met the criteria for having at least three T1-weighted images and being cognitively normal during the MRI scanning window (Fig. 1). Because changes in cortical thickness can occur several years prior to onset of cognitive impairment [18], we also excluded participants who subsequently converted from cognitively normal to mild cognitive impairment (MCI) or AD ($n = 25$). Cognitive impairment was determined by consensus diagnosis using the *Diagnostic and Statistical Manual of Mental Disorders Third Edition, Revised* (DSM-III-R) for dementia and National Institute of Neurological and Communication Disorders–Alzheimer's Disease and Related Disorders (NINDS-ADRDA) criteria for AD [19]. MCI was based on the Petersen criteria [20] and diagnosed when, first, cognitive impairment was evident for a single domain (typically memory) or, second, cognitive impairment in multiple domains occurred without significant functional loss in activities of daily living.

This study includes 96 participants (68.7 $\pm$ 7.4 years old; M = 53, F = 43) with 47 participants in the normotensive group and 49 in the HTN group (Table 1). Both groups have an average follow-up interval of 8 years with annual MRI scans. The HTN group had significantly more men than women compared with the normotensive group ($P = 0.04$). Both groups had a mean education of 16.3 years. Within the HTN group, eight participants were diagnosed with diabetes either before or during their magnetic resonance scanning window. The normotensive group also had more carriers of the apolipoprotein E (APOE) $\epsilon 4$ allele than the HTN group ($P = 0.002$). All participants gave written informed consent at each visit and the local institutional review board approved the research protocol for this study.

Hypertension status

Participants were considered hypertensive if they had a clinical diagnosis of HTN or if they had at least three visits during their imaging window while they were taking antihypertensive medication and/or had SBP higher than 140 mmHg or DBP higher than 90 mmHg. The longitudinal imaging data only included visits in which each person was either HTN or normotensive throughout the study. BP measurements and antihypertensive medication was assessed every 2 years. BP was recorded as the average of two BP measurements, one sitting and one standing, taken in the morning by a trained nursing staff equipped with an appropriately sized cuff and mercury sphygmomanometer. Within the HTN group, 31 of the participants were treated with antihypertensive medication during their MRI scanning window.

MRI acquisition, processing, and statistical analysis

All T1-weighted scans were acquired on a 1.5-Tesla GE Signa scanner using a high-resolution volumetric 'spoiled grass' series. Imaging parameters were axial acquisition, repetition time = 35 ms, echo time = 5 ms, flip angle = 45°, field of view = 24 cm, matrix = 256 $\times$ 256, voxel dimensions of 0.94 $\times$ 0.94 $\times$ 1.5 mm slice thickness.

Cortical reconstruction and volumetric segmentation were performed with the Freesurfer image analysis suite (version 5.1, <http://surfer.nmr.mgh.harvard.edu/>). Briefly, this processing includes removal of nonbrain tissue from volumetric T1-weighted images using a hybrid watershed/surface deformation procedure [21], automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (including hippocampus, amygdala, caudate, putamen, ventricles) [22,23], intensity normalization [24], tessellation of the gray matter–white matter boundary, automated topology correction [25,26], and surface deformation following intensity gradients to estimate the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class [27–29]. This method uses both intensity and continuity information from the entire three-dimensional magnetic resonance volume in segmentation and deformation procedures to produce representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/cerebrospinal fluid boundary at each vertex on the tessellated surface [29].

For longitudinal analysis, images were processed with the longitudinal stream in Freesurfer [30]. Specifically, an unbiased within-subject template space and image [31] was created

using robust, inverse consistent registration [32]. Several processing steps, such as skull stripping, Talairach transforms, atlas registration as well as spherical surface maps, and parcellations were then initialized with common information from the within-subject template, significantly increasing reliability and statistical power [30].

The resulting cortical thickness maps, 728 images in total, were smoothed along the surface with a 10-mm full-width at half maximum kernel and analyzed using a spatiotemporal linear mixed effects model in MATLAB 2013a [33,34]. This model pools spatial information in the longitudinal thickness data for each subject, guided by the biological assumption that nearby vertices will share similar temporal covariance structures for a particular linear model. We applied the following equation along every vertex of the cortex to obtain baseline and longitudinal differences in cortical thickness between groups:

$$y_{ij} = \beta_0 + \beta_1 \text{Age}_i + \beta_2 \text{Sex}_i + \beta_3 \text{Group}_i + \beta_4 \text{Interval}_{ij} \\ + \beta_5 (\text{Age}_i \times \text{Interval}_{ij}) + \beta_6 (\text{sex}_i \times \text{Interval}_{ij}) + \beta_7 (\text{Group}_i \times \text{Interval}_{ij}) + b_{0i} + b_{1i} \text{Interval}_{ij} \\ + \varepsilon_{ij}$$

(Equation 1)

In the above equation, y_{ij} denotes a vector whose elements are three-dimensional cortical thickness maps for subject i at visit j . Because previous work in our laboratory has shown cross-sectional and longitudinal effects of age and sex on cortical thickness [16], we included these covariates and their interactions with interval as fixed effects. The β s represent fixed effects estimates and the b s represent random effects estimates. This equation includes two random effects such that each person has their own unique intercept and slope. In all analyses, age was coded as each participant's mean-centered age at their first imaging visit, and sex was coded as male/female with 0.5/−0.5. Interval represents the time in years from each person's j th imaging visit and their baseline imaging visit, with their first visit coded as 0. Those in the HTN group were coded as 1 for every visit and those in the normotensive group were coded as 0. Statistical significance was based on a minimum of 200 vertices with a primary cluster-forming threshold of $P < 0.01$ and a cluster-extent threshold of $P < 0.05$.

To further investigate the extent that HTN variables could explain differences in rates of thinning between groups, we conducted an exploratory ROI analysis using all clusters larger than 200 mm² from the primary analysis as masks to extract mean thickness values at each imaging visit. Specifically, we investigated how BP at midlife, duration of HTN, and prior variability in BP related to subsequent cortical thinning. We used the same linear mixed effects model structure in Eq. (1) for each ROI and each HTN variable, in which the independent variable 'Group' is replaced with a continuous HTN variable. In separate models, we also adjusted all ROI analyses for whether any antihypertensive medication had been taken prior to baseline MRI and removed these terms from the main analyses if they were not significant. All ROI analyses were done in R version 3.1.0 using the nlme package version 3.1–117.

Midlife BP data were available in 76 participants and was determined as BP nearest to age 50, ranging from 49 to 65 years. On average, this midlife BP measurement was 12 years prior to the baseline MRI visit. Models were also adjusted for the follow-up interval between BP measurement and the baseline imaging scan. Duration of HTN data ($n = 49$) was coded as a categorical variable with two levels: history of HTN exceeding 3 years and history of HTN less than or equal to 3 years. Three years represents the median number of years with HTN in the HTN group.

Variability of BP was calculated as the intervisit standard deviation (SD) of SBP or DBP prior to each participant's baseline neuroimaging visit, requiring a minimum of three visits that assessed BP ($n = 80$). The SD was calculated for each person over an interval ranging from 4 to 9 years with 7.5 years on average (four BP measurements on average, range of 3–5). All models were adjusted for the interval over which SD was calculated.

RESULTS

To characterize differences in the rates of cortical thinning between normotensive individuals and HTNs, we applied spatiotemporal linear mixed effects models across the entire surface of the cortex. The fixed effect estimate for 'Group' in Eq. (1) represents where the cortical thickness at baseline for the HTN group is greater or less than the normotensive group. There were no significant clusters where HTNs were thinner than normotensive individuals at baseline, and one region, the right middle frontal cortex (342 mm^2), where normotensive individuals were thinner. However, this region did not overlap with any clusters that showed differences in the rates of thinning between groups.

Differences in longitudinal cortical thinning between HTN and normotensive individual

The fixed effect estimate for 'Group $\times$ Interval' in Eq. (1) represents regions where the HTN group has a different rate of thinning compared with the normotensive group. The HTN group had an increased rate of thinning in several regions (Fig. 2). Two of these regions survived a cluster-extent threshold ($P < 0.05$): the left frontomarginal gyrus ($P < 0.001$) and the right superior temporal gyrus ($P < 0.001$). In the right hemisphere, three other regions showed similar trends: the fusiform gyrus ($P = 0.054$), the lateral orbital gyrus ($P = 0.054$) and the occipital pole ($P = 0.085$) (Table 2). Any regions indicating slower rates of thinning in HTN compared with normotensive individual were small ($< 55 \text{ mm}^2$) and did not reach statistical significance.

Because of group differences in the prevalence of APOE4 and diabetes, the model was rerun while controlling for APOE status and excluding the diabetic individuals. These changes did not significantly affect the results.

Hypertension variables

To determine the relationship between HTN variables collected prior to baseline MRI and the subsequent increased thinning observed in HTNs, regions that showed an increased rate of thinning for the HTN group were used as masks to extract mean thickness values for each imaging visit. These mean thickness values were then modeled as dependent variables in mixed effects analyses. All BP analyses included participants from both the HTN and

normotensive groups and controlled for baseline and longitudinal effects of age, sex, and follow-up interval. BP analyses also controlled for usage of antihypertensive medication prior to baseline MRI in separate models; however, these treatment terms were not significant and excluded from the main models.

We found that higher midlife SBP and DBP predicted an increased rate of cortical thinning later in life in the right superior temporal gyrus ($P < 0.05$), and higher midlife SBP predicted an increased rate of cortical thinning in the lateral orbital gyrus ($P < 0.05$). No other regions showed statistical significance with midlife BP (Table 3). Prior intervisit variability in SBP was associated with thinning in the frontomarginal gyrus ($P = 0.01$), superior temporal gyrus ($P < 0.01$), and the occipital pole ($P < 0.01$), in which greater variability in SBP predicted an increased rate of thinning. High variability in DBP, however, was not associated with subsequent rate of cortical thinning. Duration of HTN was only a significant predictor of the rate of cortical thinning for the superior temporal gyrus, in which those with greater than 3 years of HTN had an increased rate of thinning compared with hypertensive individuals with less than 3 years ($P = 0.0023$).

DISCUSSION

We hypothesized the HTN group would show higher rates of longitudinal thinning compared with the normotensive group. We found that regions in the frontal and temporal cortices exhibit higher rates of thinning over time in those with HTN. Greater cortical thinning in HTN compared with normotensive individuals in the left frontomarginal gyrus and right superior temporal gyrus is consistent with previous cross-sectional findings showing a significant association between thinner superior frontal and temporal cortices and high BP [10], and with longitudinal volumetric studies showing a faster rate of cortical shrinkage in frontal volumes [1,35].

A previous study in our laboratory investigating a subsample of the current cohort showed differences in brain activity over time between HTNs and normotensive individuals using resting-state PET scans collected across a 7-year interval [36]. This study found significant longitudinal activity decreases in HTNs compared with normotensive individuals in regions that overlap with areas showing differences in cortical thinning in the current study: middle and inferior prefrontal, occipitotemporal, and posterior occipital cortex. In that study, the superior temporal gyrus was among a group of brain areas where an increase in activity over time, interpreted as a preservation of function, was significantly reduced in the HTN group. Although it is difficult to determine a causal relationship between brain atrophy and functional integrity, these data are consistent with the theory that high BP remodels blood vessels, resulting in hypoperfusion and neural death by hypoxia [37,38], which could affect both structure and function.

We did not find thinner cortex in HTNs compared with normotensive individuals at baseline as previously shown by Leritz *et al.* [10]. The difference in baseline results may reflect the short duration of HTN in our sample, with 50% of our HTN group having HTN for less than or equal to 3 years. It is possible the atrophic effects due to HTN require several years to

accrue, and that these differences would be more apparent in those who have had HTN the longest.

Midlife BP measures have historically been sensitive to detecting late-life brain atrophy in volumetric analyses [39,40], and high midlife BP appears to be a better predictor of AD risk than high late-life BP measures [41]. Our results show that high midlife SBP predicted a higher rate of thinning in the superior temporal gyrus and lateral orbital gyrus, whereas DBP predicted subsequent thinning in the superior temporal gyrus alone. Although it is known that high midlife SBP and DBP predict thinner cortex cross-sectionally decades later [11], the effect of midlife BP on the rate of late-life thinning over time has not been shown.

Our study also found that increased variability in SBP but not DBP predicted regions where HTNs thinned faster than normotensive individuals. Intervisit midlife BP variability over an interval of 6 years has been shown to be a good predictor of white matter lesions [42], and short-term intervisit BP variability has been shown to be an effective predictor of stroke and related vascular events [43]. In line with this research, our findings extend the literature in demonstrating that intervisit BP variability predicts longitudinal cortical thinning and merits consideration in understanding how HTN contributes to brain atrophy.

Finally, we found that a longer duration of HTN predicted a significantly increased rate of thinning of the superior temporal gyrus compared with those who had less than 3 years of HTN. Although Beason-Held *et al.* [36] found HTN duration to be the variable that best explained longitudinal differences in brain activation between HTNs and normotensive individuals, only one region was significantly associated with duration of HTN in the current study. The difference in findings could be due to a biological delay between early functional changes and later atrophic changes.

Our study has several advantages over previous studies investigating the relationship between brain structure and HTN. Although previous longitudinal studies of brain structure were limited to two MRI visits over a short period, our study assessed annual changes over a follow-up interval of 8 years. The long follow-up interval also allowed classification of HTN status based on at least three visits, lessening the risk of falsely categorizing someone as hypertensive due to a ‘white-coat’ effect or random fluctuation in BP. Furthermore, the current analysis excludes participants who subsequently develop MCI or dementia within the follow-up period to date, attenuating the potential effect of preclinical dementia on brain structure [18].

Due to the prospective observational nature of our study, one weakness is the inability to control for subclasses of HTN medications and/or changes in medication classes during the MRI scanning timeframe. Although some studies have shown increased brain atrophy in HTNs relative to normotensive individuals despite HTNs have controlled BP [14], others have shown a reduction in risk of hippocampal atrophy with antihypertensive treatment [35]. However, because different antihypertensive medications have unique methods of reducing BP or components of BP, they may also have unique effects on brain morphology. Another limitation is that our measure of intervisit variability in BP was based on as few as three measurements for some participants. Furthermore, each BP measurement used in our

analyses was the average of both sitting and standing measurements, and as such we did not account for possible effects of orthostatic hypotension.

A recent review [44] summarized the complex relationship between HTN and risk of dementia, cognitive decline, and possible mechanisms by which HTN manifests vascular brain injuries. Our longitudinal study design addresses key areas the review notes as important for understanding the association between HTN and brain damage, such as midlife BP and intervisit BP variability. Overall, we found significantly higher rates of cortical thinning in several areas across the cortical surface in HTNs compared with normotensive individuals. Additionally, we determined that early SBP measures compared with DBP were more likely to predict increased rates of thinning later in life, and that higher midlife BP was associated with greater subsequent thinning in the right superior temporal gyrus and lateral orbital gyrus. Our findings highlight differences in rates of cortical thinning in frontal and temporal lobes associated with HTN and suggest midlife BP and BP variability contribute to these group differences.

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Abbreviations

AD	Alzheimer's disease
BLSA	Baltimore Longitudinal Study of Aging
BP	blood pressure
CSF	cerebrospinal fluid
HTN	hypertension
MCI	mild cognitive impairment
ROI	region of interest
SD	standard deviation

References

1. Raz N, Rodrigue KM, Kennedy KM, Acker JD. Vascular health and longitudinal changes in brain and cognition in middle-aged and older adults. *Neuropsychology*. 2007; 21:149–157. [PubMed: 17402815]
2. Firbank MJ, Wiseman RM, Burton EJ, Saxby BK, O'Brien JT, Ford GA. Brain atrophy and white matter hyperintensity change in older adults and relationship to blood pressure. Brain atrophy, WMH change and blood pressure. *J Neurol*. 2007; 254:713–721. [PubMed: 17446997]
3. Skoog I, Gustafson D. Update on hypertension and Alzheimer's disease. *Neurol Res*. 2006; 28:605–611. [PubMed: 16945211]

4. Decarli C. The role of cerebrovascular disease in dementia. *Neurologist*. 2003; 9:123–136. [PubMed: 12808409]
5. Petrovitch H, White LR, Izmirlian G, Ross GW, Havlik RJ. Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS. *Neurobiol Aging*. 2000; 21:57–62. [PubMed: 10794849]
6. Raz N, Rodrigue KM. Differential aging of the brain: patterns, cognitive correlates and modifiers. *Neurosci Biobehav Rev*. 2006; 30:730–748. [PubMed: 16919333]
7. Gianaros PJ, Greer PJ, Ryan CM, Jennings JR. Higher blood pressure predicts lower regional grey matter volume: consequences on short-term information processing. *Neuroimage*. 2006; 31:754–765. [PubMed: 16488626]
8. Korf ESC, Scheltens P, Barkhof F, de Leeuw F-E. Blood pressure, white matter lesions and medial temporal lobe atrophy: closing the gap between vascular pathology and Alzheimer's disease? *Dement Geriatr Cogn Disord*. 2005; 20:331–337. [PubMed: 16179827]
9. Beauchet O, Celle S, Roche F, Bartha R, Montero-Odasso M, Allali G, Annweiler C. Blood pressure levels and brain volume reduction: a systematic review and meta-analysis. *J Hypertens*. 2013; 31:1502–1516. [PubMed: 23811995]
10. Leritz EC, Salat DH, Williams VJ, Schnyer DM, Rudolph JL, Lipsitz L, et al. Thickness of the human cerebral cortex is associated with metrics of cerebrovascular health in a normative sample of community dwelling older adults. *Neuroimage*. 2011; 54:2659–2671. [PubMed: 21035552]
11. Vuorinen M, Kåreholt I, Julkunen V, Spulber G, Niskanen E, Paajanen T, et al. Changes in vascular factors 28 years from midlife and late-life cortical thickness. *Neurobiol Aging*. 2013; 34:100–109. [PubMed: 22901697]
12. Raz N, Lindenberger U, Rodrigue KM, Kennedy KM, Head D, Williamson A, et al. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cereb Cortex*. 2005; 15:1676–1689. [PubMed: 15703252]
13. Goldstein IB, Bartzokis G, Guthrie D, Shapiro D. Ambulatory blood pressure and the brain: a 5-year follow-up. *Neurology*. 2005; 64:1846–1852. [PubMed: 15955932]
14. Jennings JR, Mendelson DN, Muldoon MF, Ryan CM, Gianaros PJ, Raz N, Aizenstein H. Regional grey matter shrinks in hypertensive individuals despite successful lowering of blood pressure. *J Hum Hypertens*. 2012; 26:295–305. [PubMed: 21490622]
15. Salat DH, Buckner RL, Snyder AZ, Greve DN, Desikan RSR, Busa E, et al. Thinning of the cerebral cortex in aging. *Cereb Cortex*. 2004; 14:721–730. [PubMed: 15054051]
16. Thambisetty M, Wan J, Carass A, An Y, Prince JL, Resnick SM. Longitudinal changes in cortical thickness associated with normal aging. *Neuroimage*. 2010; 52:1215–1223. [PubMed: 20441796]
17. Resnick SM, Goldszal AF, Davatzikos C, Golski S, Kraut MA, Metter EJ, et al. One-year age changes in MRI brain volumes in older adults. *Cereb Cortex*. 2000; 10:464–472. [PubMed: 10847596]
18. Pacheco J, Goh JO, Kraut Ma, Ferrucci L, Resnick SM. Greater cortical thinning in normal older adults predicts later cognitive impairment. (in press).
19. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDSADRDA work group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984; 34:939–1939. [PubMed: 6610841]
20. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol*. 1999; 56:303–309. [PubMed: 10190820]
21. Ségonne F, Dale AM, Busa E, Glessner M, Salat D, Hahn HK, Fischl B. A hybrid approach to the skull stripping problem in MRI. *Neuroimage*. 2004; 22:1060–1075. [PubMed: 15219578]
22. Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*. 2002; 33:341–355. [PubMed: 11832223]
23. Fischl B, Salat DH, van der Kouwe AJW, Makris N, Ségonne F, Quinn BT, Dale AM. Sequence-independent segmentation of magnetic resonance images. *Neuroimage*. 2004; 23(Suppl 1):S69–S84. [PubMed: 15501102]

24. Sled JG, Zijdenbos AP, Evans AC. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Trans Med Imaging*. 1998; 17:87–97. [PubMed: 9617910]
25. Fischl B, Liu A, Dale AM. Automated manifold surgery: constructing geometrically accurate and topologically correct models of the human cerebral cortex. *IEEE Trans Med Imaging*. 2001; 20:70–80. [PubMed: 11293693]
26. Ségonne F, Pacheco J, Fischl B. Geometrically accurate topology-correction of cortical surfaces using nonseparating loops. *IEEE Trans Med Imaging*. 2007; 26:518–529. [PubMed: 17427739]
27. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. *Neuroimage*. 1999; 9:179–194. [PubMed: 9931268]
28. Dale A, Sereno M. Improved localization of cortical activity by combining EEG and MEG with MRI cortical surface reconstruction. *J Cogn Neurosci*. 1992; 5:162–176.
29. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci U S A*. 2000; 97:11050–11055. [PubMed: 10984517]
30. Reuter M, Schmansky NJ, Rosas HD, Fischl B. Within-subject template estimation for unbiased longitudinal image analysis. *Neuroimage*. 2012; 61:1402–1418. [PubMed: 22430496]
31. Reuter M, Fischl B. Avoiding asymmetry-induced bias in longitudinal image processing. *Neuroimage*. 2011; 57:19–21. [PubMed: 21376812]
32. Reuter M, Rosas HD, Fischl B. Highly accurate inverse consistent registration: a robust approach. *Neuroimage*. 2010; 53:1181–1196. [PubMed: 20637289]
33. Bernal-Rusiel JL, Greve DN, Reuter M, Fischl B, Sabuncu MR. Statistical analysis of longitudinal neuroimage data with linear mixed effects models. *Neuroimage*. 2012; 66C:249–260.
34. Bernal-Rusiel JL, Reuter M, Greve DN, Fischl B, Sabuncu MR. Spatiotemporal linear mixed effects modeling for the mass-univariate analysis of longitudinal neuroimage data. *Neuroimage*. 2013; 81:358–370. [PubMed: 23702413]
35. Korf ESC, White LR, Scheltens P, Launer LJ. Midlife blood pressure and the risk of hippocampal atrophy: the Honolulu Asia Aging Study. *Hypertension*. 2004; 44:29–34. [PubMed: 15159381]
36. Beason-Held LL, Moghekar A, Zonderman AB, Kraut MA, Resnick SM. Longitudinal changes in cerebral blood flow in the older hypertensive brain. *Stroke*. 2007; 38:1766–1773. [PubMed: 17510458]
37. De la Torre JC. Cerebral hypoperfusion, capillary degeneration, and development of Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2000; 14(Suppl 1):S72–S81. [PubMed: 10850734]
38. Manolio TA, Olson J, Longstreth WT. Hypertension and cognitive function: pathophysiologic effects of hypertension on the brain. *Curr Hypertens Rep*. 2003; 5:255–261. [PubMed: 12724059]
39. DeCarli C, Miller BL, Swan GE, Reed T, Wolf Pa, Garner J, et al. Predictors of brain morphology for the men of the NHLBI Twin Study. *Stroke*. 1999; 30:529–536. [PubMed: 10066847]
40. Swan GE, DeCarli C, Miller BL, Reed T, Wolf PA, Jack LM, Carmelli D. Association of midlife blood pressure to late-life cognitive decline and brain morphology. *Neurology*. 1998; 51:986–993. [PubMed: 9781518]
41. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol*. 2005; 4:487–499. [PubMed: 16033691]
42. Havlik RJ, Foley DJ, Sayer B, Masaki K, White L, Launer LJ. Variability in midlife systolic blood pressure is related to late-life brain white matter lesions: the Honolulu-Asia Aging Study. *Stroke*. 2002; 33:26–30. [PubMed: 11779884]
43. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. *Lancet*. 2010; 375:938–948. [PubMed: 20226991]
44. Tzourio C, Laurent S, Debet S. Is hypertension associated with an accelerated aging of the brain? *Hypertension*. 2014; 63:894–903. [PubMed: 24566080]

FIGURE 1.

Flow chart depicting sample selection. Of the 96 participants in the primary analysis, 53 are men, aged 56–86 years. BLSA, Baltimore Longitudinal Study of Aging.

FIGURE 2.

Longitudinal differences in cortical thinning in hypertensives (HTNs) compared with normotensive individuals. Blue regions show increased rates of cortical thinning and red regions show decreased rates of cortical thinning in the HTNs compared with normotensive individuals over an 8-year period. Lateral, anterior, and medial views of each hemisphere are displayed. Only vertices with P -values between 0.01 and 0.0001 are shown.

TABLE 1

Sample characteristics

Group	HTN	NT	Total
<i>N</i>	49	47	96
Male/female ^a	31/17	21/26	53/43
Baseline age (years)	69.68 (7.5)	67.69 (7.1)	68.71 (7.4)
Mean number of scans per participant	7.41 (2.4)	7.81 (1.9)	7.6 (2.1)
Mean years of scan data per participant	7.85 (2.4)	8.1 (2.3)	7.97 (2.4)
Mean years of education	16.3 (3)	16.3 (2.4)	16.3 (2.7)
SBP (mmHg) ^a	146.0 (14.2)	125.4 (10.1)	135.8 (16.1)
DBP (mmHg) ^a	80.0 (8.5)	73.4 (6.8)	76.7 (8.4)
APOE e4 Carrier (%) ^a	14.3	42.6	28.1

^aIndicates groups were significantly different ($P < 0.05$). BP represents group averages of intervisit BP measures during imaging window for each person. APOE, apolipoprotein E; BP, blood pressure; HTN, hypertension; NT, normotensive.

TABLE 2

Clusters that show longitudinal increases in cortical thinning between hypertensives and normotensives

Brain region	Brodmann area	Cluster size (mm ²)	Cluster <i>P</i>	Peak <i>F</i> -statistic	Peak Talairach coordinates		
					<i>x</i>	<i>y</i>	<i>z</i>
Frontomarginal gyrus (LH)	11	900.40	<0.001	-12.51	-27.4	53.3	-14.7
Superior temporal gyrus (RH)	22	482.34	<0.001	-13.92	56.5	-11.8	4.5
Fusiform gyrus (RH)	19	232.94	0.054	-13.43	26.2	-54.8	-7.8
Lateral orbital gyrus (RH)	47	231.58	0.054	-9.70	47.2	36.6	-7.7
Occipital pole (RH)	18	215.03	0.085	-12.87	30.5	-91.0	1.5

Clusters indicate regions of longitudinal differences in rates of thinning between HTNs and NTs. All clusters surviving a vertex-wise primary threshold of $P < 0.01$ and exceeding 200 mm² are displayed. Regions that survived a cluster-wise correction for multiple comparisons ($P < 0.05$) have bold cluster *P*-values. HTN, hypertension; LH, left hemisphere; RH, right hemisphere.

TABLE 3

Effect of hypertension measures on the rate of cortical thinning in regions that show longitudinal differences between groups

Brain region	Midlife SBP	Midlife DBP	SD of prior SBP	SD of prior DBP
Frontomarginal gyrus (LH)	-0.23 (0.098)	-0.38 (0.075)	-0.91 (0.01)	-1.0 (0.099)
Superior temporal gyrus (RH)	-0.51 (<0.01)	-0.64 (0.017)	-1.4 (<0.01)	-0.26 (0.714)
Fusiform gyrus (RH)	-0.21 (0.123)	-0.20 (0.359)	-0.45 (0.16)	-0.89 (0.108)
Lateral orbital gyrus (RH)	-0.37 (0.015)	-0.40 (0.084)	-0.68 (0.089)	-0.04 (0.952)
Occipital pole (RH)	-0.42 (0.139)	-0.57 (0.189)	-1.8 (<0.01)	-0.89 (0.395)

β s $\times 10^{-3}$ for HTN variable $\times$ interval shown with *P*-value in parenthesis. Each BP measure and region pair was modeled separately and controlled for baseline and longitudinal effects of age, sex, and follow-up interval. Negative β s represent where unit increases in BP predict an increased rate of cortical thinning. Significant terms ($P < 0.05$) are shown in bold. BP, blood pressure; HTN, hypertension; LH, left hemisphere; RH, right hemisphere; SD, standard deviation.