Cumulative blood pressure exposure, basal ganglia and thalamic morphology in midlife

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Abstract

High blood pressure (BP) negatively affects brain structure and function. Hypertension is associated with white matter hyperintensities (WMH), cognitive and mobility impairment in late-life. However, the impact of BP exposure from young adulthood on brain structure and function in mid-life is unclear. Identifying early brain structural changes associated with BP exposure, before clinical onset of cognitive dysfunction and mobility impairment, is essential for understanding mechanisms and developing interventions. We examined the effect of cumulative BP exposure from young adulthood on brain structure in a substudy of 144 (61 female) individuals from the Coronary Artery Risk Development in Young Adults (CARDIA) study. At year 30 (Y_{30}, 9th visit), participants (56 ± 4 years old) completed brain MRI and gait measures (pace, rhythm, and postural control). Cumulative systolic and diastolic BP (cSBP, cDBP) over 9 visits were calculated, multiplying mean values between two consecutive visits by years between visits. Surface-based analysis of basal ganglia and thalamus was achieved using FreeSurfer-initiated Large Deformation Diffeomorphic Metric Mapping. Morphometric changes were regressed onto cumulative BP to localize regions of shape variation. Y_{30} WMH volumes were small, and positively correlated with

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cumulative BP, but not gait. Negative morphometric associations with cSBP were seen in the caudate, putamen, nucleus accumbens, pallidum and thalamus. A concave right medial putamen shape mediated the relationship between cSBP and stride width. Basal ganglia and thalamic morphometric changes, rather than volumes, may be earlier manifestation of grey matter structural signatures of BP exposure that impact midlife gait.

Graphical Abstract
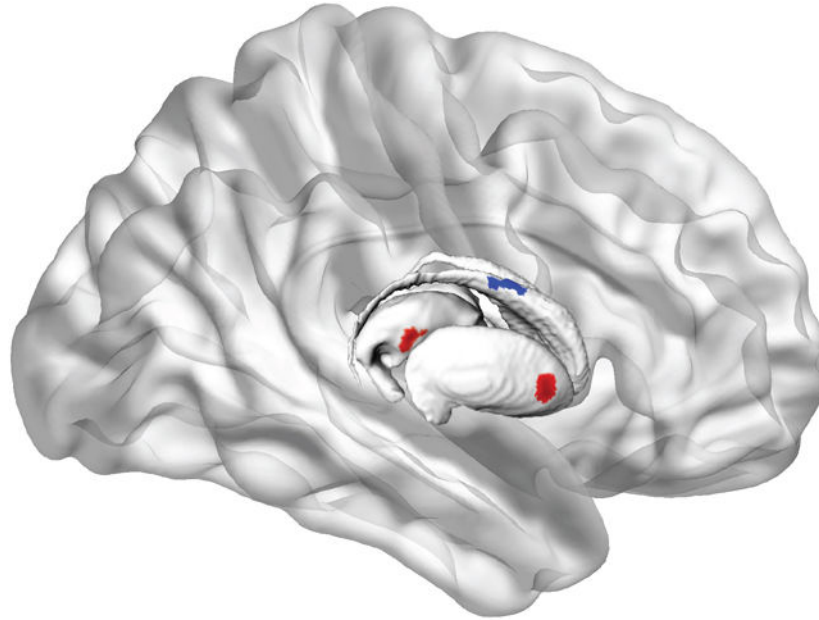
Keywords

Blood pressure; Basal ganglia; Thalamus; Middle Aged; Magnetic Resonance Imaging; Gait

The deleterious impact of high blood pressure (BP) on cognition and dementia is well established[1-4]. However, high BP is also associated with mobility impairment[5]. More importantly, gait slowing often precedes cognitive decline[6-8], suggesting that mobility changes may be an earlier marker of neurodegeneration than cognitive decline. High BP also negatively affects brain structure, and is strongly associated with white matter hyperintensities (WMH)[9], basal ganglia injury[10], as well as atrophy of subcortical structures[11]. While studies have examined the relationship between BP in midlife, brain structure, and cognition[4, 12, 13], data on the relationship between BP exposure and midlife brain structure and gait is lacking. A better understanding of preclinical structure and function changes associated with BP exposure will help elucidate underpinning mechanisms linking high BP to brain injury, and facilitate targeted therapies to preserve brain structure and prevent mobility and cognitive decline in late life.

Age-related mobility impairments have been associated with WMH[14], thalamic lacunar infarcts[14] basal ganglia volume[15], and morphology[16]. WMH, being easy to identify and grade in neuroimaging studies, have been studied widely in age-related gait disorders. While

the importance of WMH[14] can not be underestimated, age-related motor impairment cannot be entirely explained by WMH burden[17], and in fact, gray matter disturbances may have a stronger influence[18]. Disorders affecting the basal ganglia including Parkinson's and Huntington's disease are characterized by gait impairments. However, understanding the relationship between BP, WMH, basal ganglia and mobility impairment in an aged population with endstage disease has been challenging due to multiple comorbidities, accumulation of risk factors and complexity of aging. As such, we sought to explore these relationships in midlife, and to determine the early brain structural changes associated with cumulative BP exposure measured from young adulthood.

To achieve this aim, we leveraged the longitudinal Coronary Artery Risk Development in Young Adults (CARDIA) cohort. This cohort provides a unique opportunity to investigate cumulative BP exposure from young adulthood as it relates to WMH and subcortical gray matter structure in midlife. We hypothesized that BP assessed longitudinally from young adulthood would be positively associated with volumes of WMH and negatively with volumes of basal ganglia and thalamus in midlife. In exploratory analyses, we further examined whether these changes would synergistically contribute to gait changes in midlife.

Methods

Anonymized data are available from the CARDIA Coordinating Center (cardia.dopm.uab.edu/contact-cardia). The National Heart, Lung, and Blood Institute policies governing the data and describing it's access is online (https://www.cardia.dopm.uab.edu/study-information/nhlbi-data-repository-data).

Participants

The CARDIA study is a longitudinal study of cardiovascular risk factors that began in 1985 and recruited 5115 individuals aged 18-30 years. Follow-up examinations were conducted 2 (Y_2), 5 (Y_5), 7 (Y_7), 10 (Y_{10}), 15 (Y_{15}), 20 (Y_{20}), 25 ($Y2_5$), and 30 (Y_{30}) years after baseline (Y_0). Chicago is one of the 4 CARDIA field centers and all active participants from Chicago were invited to participate in this substudy (N=513). Our response rate was 71% (N=362) and 154 were willing and eligible for the MRI study. Exclusion criteria were MRI contraindications, body habitus, and suspected pregnancy. All participants provided written consent, approved by the Northwestern University IRB.

Of the 154 participants, two were excluded due to incidental stroke findings, one did not complete the T2 weighted FLAIR sequence thus did not have WMH data, one had an extreme score for WMH volume, one did not have gait assessment, one only had BP from 4 visits and four individuals were excluded due to poor segmentation of the T1 weighted image (described below), resulting in a final sample of 144 for this analysis (Table 1).

Measures

Blood Pressure—Measurement of BP has been described previously[19, 20]. Trained research staff measured BP from the right arm brachial artery while the participant was in a seated position. For Y_0 to Y_{15} a Hawksley random-zero sphygmomanometer was used, and for subsequent visits, an automated oscillometric BP monitor (Omron HEM-907XL) was

used. A calibration study standardized values to the sphygmomanometer to eliminate machine bias (see [19]). Cumulative systolic blood pressure (cSBP) was calculated per previous CARDIA studies (Yano et al., 2014, 2017), detailed in Figure 1A. Mean SBP (and mean DBP) was calculated between two consecutive visits, multipled by the number of years between those two visits, then summed to determine cSBP (and cDBP) over 30 years. cSBP and cDBP were normally distributed. All 144 participants had BP measures for Y_0 and Y_{30}, and all had BP measures for at least 5 separate visits. For Y2, Y5, Y7, Y10, Y15, Y20, and Y25, BP data were unavailable for 3, 4, 10, 7, 2, 3 and 2 participants, respectively.

Gait—Gait was measured during a 40-foot walk on a 20×2 foot Zeno walkway. Data were captured with Prokinetics Movement Analysis Software, which has established reliability and validity[21]. Participants walked at their normal pace. The most frequently reported gait variables in the related to the gait domains of pace, rhythm and postural control were measured[22, 23]. Velocity (pace domain) is reported as centimeters per second. Cadence (rhythm domain) is reported as steps per minute. Stride width (postural control domain) is defined as the perpendicular distance of a line connecting two heels from the same foot and the heel of the contralateral foot. This value can be negative in out-toe walking individuals whos heels overlap when they land.

Image acquisition and surface mapping

A 3T Siemens Prisma MRI scanner was used to collect T1-weighted Magnetization prepared rapid gradient echo (MPRAGE) images in the sagittal plane. Voxels resolution was $0.98 \times 0.98 \times 1.0$, slices=176, FOV=$256 \times 256$, TR=1900, TE=2.93, TI=900, flip=9. T2-weighted FLAIR images were also collected in the sagittal plane with the same voxel resolution, slices and FOV, with a TR=1900, TE=2.93 and TI=900. WMH volume was calculated by manually delineating hyperintense voxels on FLAIR weighted images using Freeview by research assistants (S.K. and J.H) blinded to the other study data and under the supervision of T.P. Cases where there were any uncertainties were reviewed by a neuroradiologist (A.N.). WMH values were normalized by each participant's intracranial volume (ICV) and multiplied by 1000. A log transformation was applied to achieve normality, and correlations with both the normalized and log transformed normalized results are reported.

Regions of interest (ROIs) were bilateral nucleus accumbens, caudate, putamen, pallidum and thalamus. ROI surfaces were automatically generated for each participant using the FS +LDDMM pipeline[24]. This combines FreeSurfer's (FS) probabilistic voxel-based classification and a deformable, high dimensional template-based method of large deformation diffeomorphic metric mapping, (LDDMM)[25]. FreeSurfer (version 5.3) subcortical labeling for the initial basal ganglia segmentations was followed by image alignment and intensity normalization with LDDMM[25], which produces smooth transformations for each ROI.

Surface processing

Each participant's surface was rigidly registered to atlas space to calculate a population average. For each participant, local shape variation[24] was calculated from the population average by quantifying the perpendicular amplitude between surfaces at a vertex-to-vertex

level. The quantification of perpendicular change between surfaces was assigned a positive (outward variation from population average) or negative (inward variation from population average) value. For each ROI, shape variation values at each vertex were summed across the whole surface. Overall volume for each participant for each ROI was calculated utilizing the volume enclosed within the surfaces.

Statistical Analysis

Associations between cSBP (or cDBP) and volume of each ROI were examined using partial correlations, controlling for age, sex, race and ICV. We examined associations between cSBP (or cDBP) and local shape variation of each ROI in surface-based analyses using SurfStat[26] implemented in MATLAB. To localize regions of local shape variation, multivariate linear regression models evaluated the associations of cSBP with morphometric changes. Separate models were tested for each of the five ROIs, adjusting for age, sex, race and ICV in all models. To account for multiple comparisons within each ROI ($p < 0.001$), Random Field Theory (RFT; [27]) was applied using SurfStat. This approach provided clusters of vertices at the desired family-wise error rate (FWER) of $p < 0.05$ per ROI. Significance and direction of association were visualized as a color map on the overall average surface.

Exploratory analyses

We were additionally interested in understanding if the multiple comparison corrected, morphological associations with cSBP were also related to gait. Therefore we undertook further exploratory analyses of three measures of gait. To reduce the number of mediation analyses performed, therefore the number of statistical comparisons, we first calculated bivariate correlations (uncorrected) to identify morphometric clusters that were associated with gait (Figure 1). Mediation analyses using ordinary least squares path analysis were conducted using PROCESS[28] for SPSS to determine whether deformities negatively associated with cSBP mediated relationships between cSBP and gait. Age, sex, race and ICV covariates were included in the models. Given that our sample did not yet demonstrate substantial WMH burden[29], and in line with previous research examining the relationship between basal ganglia and gait[15], we chose to covary WMH volume, along with other risk factors of Y_{30} BMI, Y_{30} cholesterol (mm/dL), Y_{30} self-reported diabetes, and Y_{30} self-reported smoker. Multicollinearity was assessed and found to be absent, with tolerance values ranging from 0.51 to 0.94 and variance inflation factor values ranging from 1.07 to 2.00. 95% confidence intervals were estimated using 5000 bootstraps. We hypothesized that inward morphology of regions associated with cSBP would mediate the relationship between cSBP and gait performance.

Results

Demographic data are summarized in Table 1. Our mid-life sample, without a substantial burden of vascular risk factors, is representative of the CARDIA participants in the Chicago cohort.

BP exposure and Brain Structure in midlife

As expected, we observed positive partial correlations between cSBP and cDBP (0.80, $p<0.0001$), cSBP and WMH volume (0.21, $p= 0.01$), and log WHM volume (0.23, $p= 0.007$), cDBP and WMH volume (0.18, $p= 0.04$), and log WMH volume (0.20, $p= 0.01$). Surprisingly, there were no correlations ($p> .05$) between cSBP or cDBP and any grey matter volumes. WMH volume was negatively correlated with volume of the left pallidum (−0.18, $p= 0.04$), however not after FWE correction for multiple comparisons ($p> .05$).

Morphometry results are presented in Figure 2. Red indicates regions of negative associations with cSBP (inward deformity associated with increased cSBP), and blue indicates regions of positive associations with cSBP (outward deformity associated with increased cSBP). Negative associations were observed for the left lateral caudate head and lateral nucleus accumbens, right medial and lateral putamen, lateral thalamus and lateral anterior pallidum. A positive association was also found on the right lateral caudate body. Because this region abuts the ventricles, it is highly susceptible to WMH. Visual inspection confirmed that observed positive associations were, in fact, the result of segmentation errors by the automated pipeline. This pipeline uses T1 weighted images to segment subcortical structures, and since WMH appear hypointense on T1 weighted images, they are misclassified as gray matter.

A sensitivity analysis additionally covarying handedness replicated Figure 2, without the pallidum, thalamus or lateral putamen clusters, or the positive caudate cluster. There were no associations between cDBP and morphometry, after covariate adjustment, at the FWE corrected threshold.

Exploring gait in midlife and cSBP-related morphological changes

Gait velocity in the entire sample ranged from 77 to 181cm/second (125± 19). Cadence ranged from 79 to133 steps/minute (107±10). Stride width ranged from −2 to 17cm (8±3).

Bivariate correlations between inward clusters and gait measures are presented in Supplemental Table S1. Positive correlations were observed between velocity and the large nucleus accumbens and thalamic clusters, and negative correlations were found between stride width and caudate, pallidum and medial putamen clusters. These four clusters were subsequently examined as potential mediators of the relationship between cSBP and gait. WMH volume was not correlated with any gait measures ($p> .05$). Partial correlations found cBP were not correlated with gait measures after controlling for cardiovascular risk factors (Supplemental Table S2). However, the total effect of X (cSBP) on Y (gait) should not be a prerequisite for searching for indirect (mediating) effects[28].

Participants with higher cSBP had greater mean inward deformity of the medial putamen (a= −0.0003, p=0.0031, CI −0.004 to −0.001), and participants with greater inward deformity of the medial putamen had wider strides (b= −3.3508, p= 0.0055, CI −5.7012 to −1.003) (Figure 3). There was no evidence that cSBP influenced stride width independently of its effect on medial putamen deformity (c'= −0.0023, p= 0.07, CI= −0.0048 to 0.0002). A bootstrap 95% confidence interval for the indirect effect of cumulative SBP on stride width through mean medial putamen deformity (ab= 0.0009) based on 5,000 bootstrap samples

was above zero (0.0002 to 0.0020). These results suggest that the relationship between cSBP and stride width may be mediated through medial putamen deformity. Other deformities negatively associated with cSBP did not mediate the relationships between cSBP and gait (Supplemental Table S3).

Discussion

We show that cumulative BP exposure over 30 years from young adulthood is associated with morphological changes of the basal ganglia and thalamus in midlife. cSBP was associated with inward deformity in the left lateral caudate head and lateral nucleus accumbens, the right lateral pallidum and thalamus and the medial and lateral putamen. cDBP exposure was not associated with morphometry despite a strong relationship (r=0.80) with cSBP. In exploratory analyses, inward deformities of basal ganglia and thalamic structures predicted by longitudinal cumulative BP exposure were positively correlated with velocity and negatively correlated with stride width. Moreover, these exploratory analyses found that the relationship between cSBP and stride width was mediated by inward deformity of the medial putamen. Our findings suggest that morphometric changes of the basal ganglia and thalamus which could impact gait and mobility, may be early structural signatures of cBP exposure in the brain.

Our middle-aged sample with vascular risk factors, but without a high burden of overt hypertension, are likely at a preclinical, early stage of pathology. We argue that this accounts for the lack of correlations between cBP exposure and basal ganglia and thalamic nuclei volumes. However, the subtle morphological findings which require a precision that is not apparent on standard grey matter volumetric analysis[30], reveal regional shape disparities in relation to cumulative BP exposure. Thus, our more sensitive vertex-wise analyses show that cSBP, but not cDBP exposure, across young adulthood is related to midlife inward deformity of subcortical structures known to be central to control of gait and posture. These findings are consistent with a meta-analysis where the association between high BP or hypertension and brain volume was mostly driven by SBP rather than DBP[11]. Our results are also consistent with Goldstein et al.[31] who report that in healthy adults (aged 56-80) without a diagnosis of hypertension, those with higher BP were more likely to have brain atrophy than those with lower BP.

The inward morphometric changes related to cSBP exposure are also in line with previous studies that did not measure gait, but did examine the relationship between subcortical atrophy and hypertension. For example, these studies show thalamic atrophy in midlife and late-life adults with hypertension[32] and even adults (aged 35-65) that were successfully treated for hypertension[33], as well as hippocampal atrophy in otherwise healthy adults (aged 20-77) with hypertension[34] and in males in late life who had uncontrolled hypertension in midlife[35]. While there is also data showing an absence of association between a diagnosis of hypertension and basal ganglia volumes[36], in one study, SBP> 140 was associated with a steeper decline in basal ganglia volumes over 2.4 years[37]. Our study extends this literature and shows that cumulative BP exposure-related morphometric changes can be observed as early as midlife. In addition, our study underscores the importance of longitudinal BP measurement rather than a single measure or a clinical diagnosis of hypertension in

understanding the impact of BP on brain structure. Further longitudinal data will help us determine if these early morphometric changes are related to later volume loss in these structures.

In our exploratory correlation analyses, we found that inward basal ganglia and thalamic morphological deformations were associated with lower velocity and greater stride width, supporting previous findings linking elevated BP with lower gait speed[38]. However, in our midlife cohort, WMH volumes were not correlated with gait measurements. This finding does not support previous reports that WMH are associated with gait, even after controlling for vascular risk factor[14, 39]. However, these prior studies were conducted in late-life cohorts with a greater duration of exposure to cumulative vascular risk factors and a higher burden of WMH than the individuals in midlife assessed in our study. WMH likely represent more advanced injury and manifest with more severity of gait impairment. Studies that have found associations between gait speed and atrophy of the hippocampus[40-42], caudate[15] or putamen[40] also tend to differ in demographics from the midlife sample we studied here. Our midlife sample has had a shorter exposure to vascular risk factors than cohorts in later life and less time to develop age-related changes in brain structure and function, offering the advantage of allowing us to study earlier signatures of BP exposure on the brain structures important in mobility.

Exploratory analyses found that inward deformation of the medial putamen associated with higher cSBP exposure mediated the relationship between cSBP and stride width. While this small effect isn't likely to have immediate clinical relevance, we contend this is an early change likely to worsen with increased cSBP exposure. It's also congruent with clinical observations. Widening of base of support is a compensatory mechanism to maintain balance in those with age-related mobility impairment and in patients with normal pressure hydrocephalus[43]. A study of elderly, non-disabled adults with WMH found inward left caudate deformation was associated with lower performance on the Short Physical Performance Battery[16]. Structural changes in the putamen have also been linked to balance and mobility in older adults[44] and those diagnosed with Alzheimer's disease[45]. Similarly, in older adults, reduced gray matter in the pallidum was also associated with wider step[46]. Stride base widening may be an early measure of compensation for at-risk adults who do not manifest overt cerebrovascular disease and/or mobility impairment.

Studying individuals in midlife provided us an opportunity to study relationships between longitudinal measures of BP, structural brain changes, and gait in an early stage of injury. Our main findings are that cSBP was associated with WMH and predicted local inward morphometric changes in deep gray nuclei. Exploratory analyses suggest that these inward shape changes in the medial putamen mediated the relationship between cSBP and stride width, even when controlling for other vascular risk including WMH volume. The complexity of age-related comorbid risk factors makes it difficult to disentangle the longitudinal sequence of structural changes that impact gait in the elderly. For example, in a late-life cohort, de Laat et al.[47] suggested that WMH may lead to secondary neuronal degeneration of gray matter regions involved in gait control. Conversely, Su et al.[17] conducted a mediation analysis and found that thalamic atrophy mediated the effect of WMH on walking speed in elderly adults with cerebral small vessel disease. Clearly,

longitudinal data on individuals from mid-life with detailed vascular, gait and brain measures are needed before we can answer this question.

Our study has some limitations. While our focus on the basal ganglia and thalamus is supported by prior work[15], our analyses did not include cortical brain regions or the cerebellum, which may also contribute to mobility and gait in midlife. We used the automated FSLDDMM pipeline, and while this approach has advantages over manual tracing methods, WMH appear to have led to some segmentation errors. Studies utilizing such pipelines in WMH-prone populations, albeit in midlife, before there is a substantial burden of WMH volume, should consider this limitation. The cross-sectional neuroimaging data precludes inference as to when the morphological changes that were associated with BP occurred. More frequent longitidunal neuroimaging data are needed to delineate the time course of these basal ganglia and thalamic morphological changes. The longitudinal BP measurements collected at 9 time points were a strength of the study, however, levels of BP control in between visits are unknown, potentially confounding results. Other measures of BP such as BP variability may also have contributions, however, we had to limit the number of analyses feasible in our sample. Unlike the main neuroimaging results, exploratory analyses linking gait to structural brain changes related to cSBP were not corrected for multiple comparisons. Therefore, while our exploratory findings offer support for previous research, they underscore the need for future larger studies powered to directly examine these relationships more closely.

Summary and Conclusions

Our study identifies a relationship between cSBP exposure and morphology of the caudate, putamen, pallidum, thalamus and nucleus accumbens in midlife. We show that in midlife, inward deformity of these regions is associated with cSBP exposure and mobility. Morphometry may prove to be a more sensitive early brain measure of BP exposure than volume, and a useful biomarker to identify individuals at risk of functional decline. Earlier identification of at-risk individuals is essential for preventing silent brain changes which later manifest as overt cognitive and mobility impairment in our aging population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Perspectives

Hypertension is a well-established risk factor that negatively impacts brain health later in life. Specifically, hypertension is associated with structural changes in the brain seen on MRI as white matter hyperintenisties (WMH), mobility impairment and cognitive dysfunction in elderly people. However, we know very little about earlier brain structure and function manifestations that may be associated with higher blood pressure exposure, before there is clinical decline in brain health. Identifying early brain structural changes associated with blood pressure (BP) exposure, before the clinical onset of cognitive dysfunction and mobility impairment, is essential for understanding mechanisms and developing interventions. In this study, we examined the effect of cumulative BP exposure from young adulthood on brain structure in 144 (61 female) individuals from the Coronary Artery Risk Development in Young Adults (CARDIA) study with 9 clinical assessments between 1985 and 2015. At year 30 (Y_{30}, 9th visit), participants (56±4 years old) completed brain MRI and gait measures (pace, rhythm, and postural control). While Y_{30} WMH volumes were small in this age group, they were positively correlated with cumulative BP exposure, but not gait. Higher cumulative BP exposure was also associated with negative morphometric changes seen in the caudate, putamen, nucleus accumbens, pallidum and thalamus. Moreover, a concave right medial putamen shape mediated the relationship between cumulative SBP and stride width. Our findings suggest that morphometric changes of the basal ganglia and thalamus, which could impact gait and mobility, may be early structural signatures of cumulative BP exposure in the brain.

Novelty and Significance

What is new:

Morphometric changes of basal ganglia and thalamic nuclei in midlife, before substantial WMH accumulation, may be an early structural signature of brain injury in those with a higher exposure to BP during young adulthood.

What is relevant:

Indiviudalized, *early* BP control targeted to preserve brain structure is an essential step towards preventing silent brain changes which later manifest as overt cognitive and mobility impairment in our aging population.

Summary

Higher cumulative exposure to SBP starting in young adulthood is associated with morphometric changes in basal ganglia and thalamus, measured in midlife. Exploratory results suggest these morphometric changes may be related to early gait changes in a cognitively normal cohort in midlife.
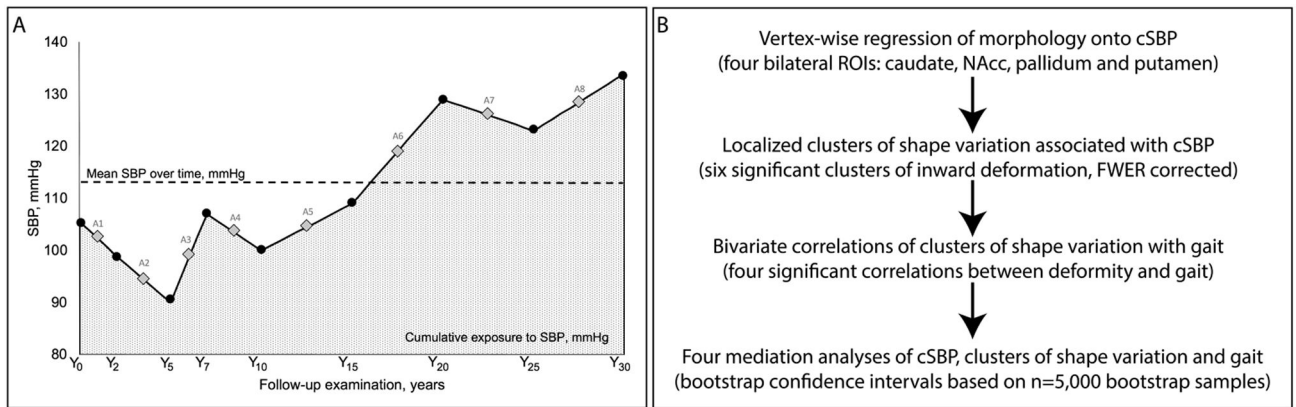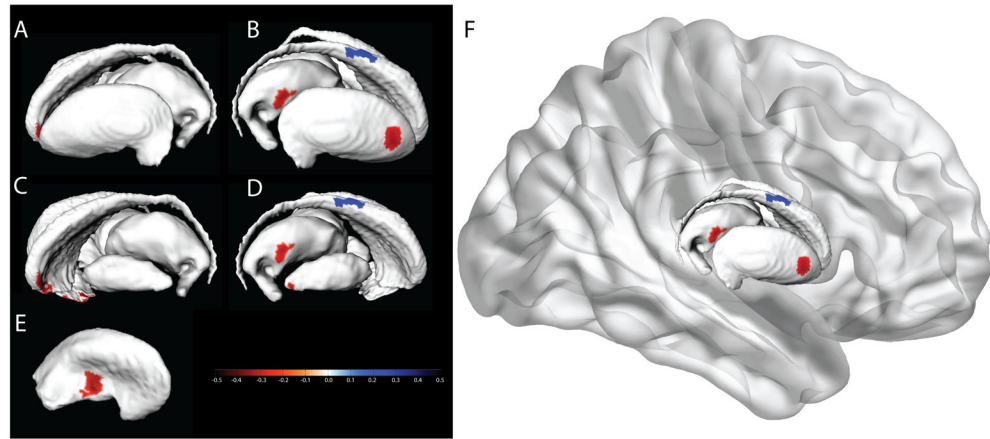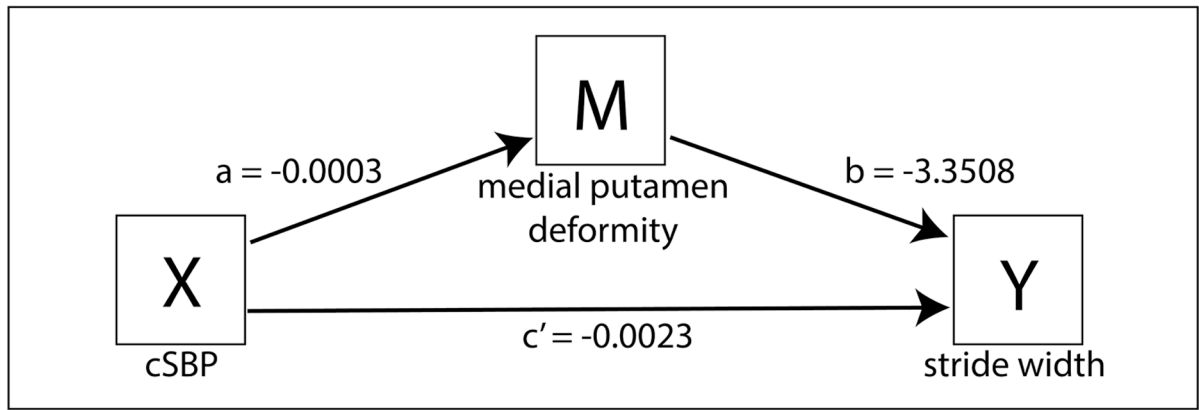
Figure 1.
A) (Adapted from Yano et al., 2017) cSBP calculation across 9 visits in one participant. Average SBP between consecutive visits is shown as A1-A8. cSBP was calculated as (A1 x 2 years + A2 x 3 years + A3 x 2 years + A4 x 3 years + A5 x 5 years + A6 x 5 years + A7 x 5 years + A8 x 5 years), shown by the dotted area, mm Hg x years. **B)** Statistical analysis for the study.

Figure 2. Surface deformities related to cumulative SBP.
a) left lateral basal ganglia/thalamus, **b)** right lateral basal ganglia/thalamus, and occluded structures of **c)** left lateral caudate, nucleus accumbens, thalamus **d)** right lateral pallidum, **e)** right medial putamen, **f)** the basal ganglia *in situ*. Scale shows standardized regression coefficients.

Figure 3.
Mediation analysis: Indirect effect of cSBP on stride width through medial putamen deformity. Values are unstandardized regression coefficients. See text for statistics and interpretation.

Table 1

Demographic variables and cardiovascular risk factors at Y_{30}

Variables	Mean (SD) or n
Sex	83 Male, 61 Female
Race	88 White, 56 Black
Age (years)	56 (4) [range=48-63]
Education (years)	15 (3)
Handedness	123 Right, 21 Left
Intracranial volume (mm^3)	1,520,406 (146,767)
Cumulative SBP (mmHg in 30 yrs)	3,284 (256)
Cumulative DBP (mmHg in 30 yrs)	2,064 (206)
Y_0 SBP (mmHg)	107 (10)
Y_0 DBP (mmHg)	65 (10)
Y_{30} SBP (mmHg)	118 (14)
Y_{30} DBP (mmHg)	72 (10)
Body Mass Index	28 (4)
Self-reported hypertension	104 No, 40 Yes
Self-reported diabetes	131 No, 13 Yes
Glucose Y_{30} (mg/dL)	99 (18)
Self-reported high cholesterol	94 No, 50 Yes
Cholesterol Y_{30} (mm/dL)	196 (37)
Self-reported smoker	123 No, 21 Yes
Taking diabetes medication Y_{30}	132 No, 12 Yes
Taking BP medication Y_{30}	114 No, 30 Yes
Taking cholesterol medication Y_{30}	119 No, 25 Yes