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Pulse pressure trajectories predict brain microstructure in community-dwelling older adults: Associations with executive function and modification by *APOE*

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Abstract

INTRODUCTION: Effects of chronic arterial stiffness on brain aging remain unclear. We therefore examined whether long-term trajectories of pulse pressure (PP) predicted brain microstructure, microstructure mediated PP-executive function associations, and *APOE* genotype modified PP-microstructure associations.

METHODS: We examined associations of PP trajectories with brain microstructure measured using restriction spectrum imaging in 146 community-dwelling older adults, whether microstructure mediated PP trajectory-executive function associations, and whether PP-RSI correlations were modified by *APOE*-ε4 status.

RESULTS: Participants with trajectories of high PP had lower restricted isotropic diffusion (RI) compared to those with low PP trajectories and PP-executive function associations were mediated

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Conflict of interest: The authors declare they have no conflict of interest.

Compliance with Ethical Standards

Ethical standards: All procedures performed in the Rancho Bernardo Study of Healthy Aging involving human participants were in accordance with the ethical standards of the Institutional Review Boards of the University of California, San Diego and were in compliance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the San Diego State University Institutional Review Board.

Ethical approval: Informed consent was obtained from all individual participants included in the study.

by subcortical and white matter RI. High PP more strongly correlated with lower RI and higher hindered diffusion among *APOE*-ε4 carriers than non-carriers.

DISCUSSION: Prolonged elevated PP predicts microstructural abnormalities which may contribute to impaired executive function. *APOE*-ε4 carriers may be most vulnerable to the adverse effects of PP on brain microstructure.

Keywords

blood pressure; pulse pressure; diffusion MRI; aging; cognitive function

INTRODUCTION

A long preclinical period precedes the onset of cognitive decline and dementia, with mounting evidence that midlife is a critical window for minimizing the impact of vascular risk factors on cognitive decline [1]. The age-related arterial stiffening that begins around midlife is hypothesized to play a central role in brain aging [2], as increased pulsatility of the brain's microvasculature [3] can disrupt cerebrovascular function and induce microbleeds [4] and ischemia [5], which may result in cumulative pathology that impairs cognitive and brain function. Prospective epidemiologic studies have reported that midlife pulse pressure (PP) or pulse wave velocity, proxy measures of arterial stiffness, predict cognitive decline [6–10] and dementia risk [10–14], however, effects of prolonged arterial stiffness prior to cognitive symptom onset remain unclear. Associations of PP with brain and cognitive outcomes are particularly pronounced among individuals carrying the apolipoprotein E (*APOE*) ε4 allele, the strongest genetic risk factor for sporadic AD [15]; higher PP better predicts brain atrophy and cognitive decline [16–18], and more strongly correlates with amyloid burden [19], for *APOE* ε4 carriers that non carriers. Characterizing effects of chronic arterial stiffness on neurobiological aging, and identifying those most vulnerable to its adverse consequences, could prove pivotal for personalized therapeutic approaches to preserve brain health.

The cognitive domains that appear to be affected by arterial stiffness include attention [20], memory [6,20], language [21], and executive function [20]. Consistent with this literature, in the Rancho Bernardo Study (RBS) a 10 mmHg increase in PP was associated with a 9% increase in the odds of low performance on the Halstead-Reitan Trail Making Test Part B (Trails B), a test of visuomotor tracking and executive function [22], among participants younger than 80 years [23]. Despite accumulating evidence for a potentially causal role for PP in the pathology of cognitive decline, the neurobiological mechanisms appear complex and warrant further examination using methods optimized to detect subtle cytoarchitectural brain abnormalities.

Multicompartment diffusion models such as restriction spectrum imaging (RSI) [24], which characterizes cellular microstructure by quantifying the magnitude and direction of water diffusion among distinct tissue compartments, are well suited to detect early neural injury. We previously reported that RSI is highly sensitive to subtle cytoarchitectural changes associated with cognitive function in normal aging [25] and prodromal AD [26]. Among a sample of cognitively-normal adults of the RBS, PP at the time of MRI correlated with

lower restricted isotropic diffusion, a measure of intracellular integrity, in global white matter and subcortical regions [25].

Herein, we extend our previous cross-sectional work by considering repeated assessments of blood pressure to evaluate lifespan PP trajectories relative to microstructural brain integrity among a sample of community-dwelling older adult RBS participants free of dementia. This study had three primary aims: First, we characterized PP trajectories from midlife to older age to examine whether lifespan PP trajectories predict brain microstructure. Second, we evaluated the clinical relevance of observed microstructural abnormalities by assessing if they mediated cognitive function. Third, we examined whether *APOE* genotype modified PP-microstructure correlations to determine whether effects of PP on brain microstructure differed according to AD genetic risk.

METHODS

Study Population

Participants were from the RBS, a community-based cohort of older adults established in 1972–1974 to identify cardiovascular, metabolic, and cognitive aging risk factors, with follow-up visits approximately every four years since enrollment through 2016 [27]. Of the 221 RBS participants alive and eligible to participate in this study, we included 154 men and women who underwent an MRI assessment in 2014–2016 and met inclusion criteria including no safety contraindication for MRI and no history of stroke, neurological disease, head injury, or treatment for an alcohol use disorder. We excluded six participants due to poor MRI data quality, one participant who had severe white matter disease, and one participant who had a Mini-Mental State Examination (MMSE) score <24 (derived from the Modified Mini-mental State-Exam, 3MS, as described below) resulting in an analytic sample of 146 participants.

Study procedures were approved by the UC San Diego Institutional Review Board and all participants provided written informed consent prior to participation.

Imaging Data Acquisition and Processing

Details of the MRI data acquisition and processing have been previously described [28]. All MRI procedures occurred at the University of California, San Diego Center for Functional MRI. MRI assessment was done using 3.0 Tesla Discovery 750 scanner (GE Healthcare, Milwaukee, WI, USA) with an eight-channel phased array head coil. The MRI sequence included a three-plane localizer; a sagittal 3D fast spoiled gradient echo T1-weighted volume optimized for maximum gray/white matter contrast (TE=3.2ms, TR=8.1ms, inversion time=600ms, flip angle=8°, FOV=24cm, frequency=256, phase=192, voxel size=1×1×1.2 mm, scan time 8:27); and an axial 2D single-shot pulsed-field gradient spin-echo echo-planar imaging sequence (45-directions, b-values=0, 500, 1500, 4000 s/mm2 and 15 gradient directions for each non-zero b-value; TE=80.6ms, TR=8s, frequency=96, phase=96, FOV=24cm, slice thickness=2.5mm, scan time 6:34).

The MRI data were processed using FreeSurfer (http://surfer.nmr.mgh.harvard.edu) with in-house Matlab scripts, as previously described [29]. Gray and white matter and cerebrospinal

fluid boundaries were delineated on high-resolution T_1-weighted structural images and subcortical regions were segmented based on a probabilistic atlas [30]. RSI data were registered to the T_1 volume using mutual information after coarse pre-alignment to atlas brains. Using probabilistic atlas-based tract segmentation (AtlasTrack [31]), individual white matter fiber path streamlines were traced and labeled by comparing DTI-derived diffusion orientations to atlas fiber orientations.

Computed RSI metrics included restricted isotropic diffusion (RI), neurite density (ND), hindered isotropic diffusion (HI), and isotropic free water (IF). RI reflects small spherical spaces such as cell bodies or synapses. ND measures oriented restricted diffusion while accounting for crossing fibers, and reflects the intracellular compartment attributable to dendrites and axons. HI reflects the extraneurite fraction or large cell bodies. IF predominantly reflects cerebrospinal fluid. All RSI metrics were computed in five subcortical regions including the hippocampus, caudate, putamen, thalamus, and amygdala. Because fiber architecture is poorly characterized by the hindered fraction, HI was not examined in white matter tracts. All other RSI metrics were computed in 15 white matter fiber tracts. Cortical gray matter was not examined, given our previously reported associations between PP and subcortical and white matter, but not gray matter, microstructure [25]. To assess potential contributions of atrophy to microstructural measures, volume in subcortical regions and across all white matter were computed and adjusted for total intracranial volume.

Cognitive Assessment

Cognitive function was assessed at time of MRI using a battery of standardized neuropsychological tests including the 3MS and Trails B. The MMSE is a measure of global cognitive function and a brief, objective screening measure of dementia with a maximum score of 30 points [32] and the 3MS is an expanded version of the MMSE designed to permit derivation of the MMSE score [33]. As MMSE scores below 24 indicate moderate cognitive impairment [34], this cutoff was used to exclude individuals with suspected dementia. Trails B [22] assesses executive function and consists of 24 circles on a piece of paper with half the circles containing the numbers 1–12 and the other half containing the letters A-L. Participants are asked to draw lines connecting the circles in ascending order, alternating between connecting numbers and letters. Trails B performance is evaluated by the time required to complete the test, with a maximum completion time of 300s. Thus, higher scores indicate poorer performance.

Pulse Pressure Assessment

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured at a maximum of eight clinic visits from 1984–2016, over a mean follow-up period of 23.6 (minimum=4.9, maximum=31.5) years, by a nurse certified in the Hypertension Detection Follow-up Protocol [35]. At each clinic visit, two blood pressure readings were taken at least 30 seconds apart using a regularly calibrated standard mercury sphygmomanometer after having participants sit quietly for five minutes. The two SBP and two DBP measurements were averaged and PP at each clinic visit was calculated as the difference between SBP and DBP (i.e., SBP–DBP). Use of anti-hypertension medications (yes or no) including calcium

channel blockers, beta blockers, vasopressors, or diuretics, was validated at each clinic visit by a nurse who examined containers and prescriptions brought to the clinic.

Covariate Assessment

Potential confounders of associations between PP and brain microstructure or cognitive function were obtained by self-report and included age (years), sex (male or female), education (years), alcohol consumption (non-drinker or drinker in the past year) and frequency (1 or more times per week or less than 1 time per week), smoking status (never or former/current smoker), exercise 3 times per week (no or yes), body mass index calculated from height and weight (kg/m^2), history of cardiovascular disease including angina, heart attack, congestive heart failure, atrial fibrillation, stroke, or transient ischemic attack (no or yes), and history of diabetes (no or yes). Genotyping of the apolipoprotein E locus (*APOE*) was done using the Illumina Global Screening Array (Illumina, Inc., San Diego, CA) on genomic DNA extracted from whole blood samples. Participants were dichotomized as *APOE* ε4 carriers (ε3/ε4 or ε4/ε4; there were no ε2/ε4) or ε4 non-carriers (ε2/ε3 or ε3/ε3).

Statistical Analysis

We employed latent class growth modeling [36] to identify groups of participants with distinct long-term PP trajectories based on a PP measurements made from 1984 to 2016. PP was modeled as a function of age using a censored normal model with linear, quadratic, or cubic terms and with adjustment for time-varying use of anti-hypertension medications. We determined the best-fitting solution by comparing the Bayesian Information Criterion (BIC) values for two- and three-group models; a lower BIC indicates a better fitting model. After participants were assigned to their PP trajectory group, we examined differences in demographic characteristics by PP trajectory group using χ^2 tests for categorical variables and independent samples t-tests for continuous variables.

To determine whether PP trajectory predicted brain microstructure, we used multiple linear regression to examine associations between PP trajectory group and each RSI metric per one-standard deviation increase. Base models were adjusted for age and sex. To determine if associations were attributable to atrophy, sensitivity analyses further adjusted for volume in the respective subcortical region or across global white matter for fiber tracts (all volume measures adjusted for intracranial volume). We also examined statistical interactions between PP trajectory and *APOE* status in base models. Fully-adjusted models additionally included covariates that were *a priori* selected as potential confounders of the associations between PP trajectories and brain microstructure.

To further probe modifying effects of *APOE* genotype on associations between PP and microstructure, we computed partial correlations (*r*), adjusted for age and sex, between continuous PP at the time MRI metrics were collected, stratified by *APOE* status. Partial correlations between *APOE ε4* carriers and non-carriers were compared using Fisher *r*-to-*Z* transformations.

We used linear regression to examine the association between PP trajectory and Trails B performance. To examine the mediating role of RSI metrics on the association between

PP trajectory and Trails B performance, we used the MacKinnon approach [37]: using linear regression, we estimated associations between PP trajectory and each RSI metric (a-pathway); associations between each RSI metric and Trails B performance, adjusting for PP trajectory group (b-pathway); and the product of the two (a*b pathway), which reflects the indirect effect of PP trajectory group on Trails B performance via RSI. Mediation exists if $\beta_a * \beta_b$ is larger or smaller than 0 and if 95% bias-corrected bootstrap ($boot$=10,000) confidence limits, estimated using the SAS PROCESS macro [38], excludes 0.

Analyses were conducted using SAS Version 9.4 (SAS Institute Inc., Cary, NC). Because of the multiple brain regions examined, a threshold of $P<0.01$ was set to determine statistical significance for associations between PP and microstructure. After selecting regions demonstrating a statistically significant association, significance for mediation analyses and for comparing correlation strengths by $APOE$ status was set to $P<0.05$.

RESULTS

Participant characteristics

Characteristics for the 146 study participants are reported in Table 1. Mean age at time of MRI was 76.6 (SD=6.8) years. The majority of participants were female (61.6%), never smoked (58.9%), consumed alcohol (85.5%), and had no history of cardiovascular disease (87.7%), and 23.2% were $APOE$ ε4 carriers. Compared to the overall RBS sample of participants who were alive and eligible for study participation, those included in the analytic sample were similar in most characteristics, but were more likely to be female (61.6% vs. 55.7%) and were less likely to have a history of cardiovascular disease (12.3% vs. 20.4%).

The majority of participants (92%) had four or more PP measurements. Latent class modeling determined that a two-group model provided an optimal fit, resulting in two PP trajectory groups. Although PP increased with age at similar rates for both groups, participants separated according to consistently lower or higher PP than expected for age. For the predicted low PP trajectory group (n=96), PP increased from 34.42 mmHg at age 51 years to 50.4 mmHg at age 77 years and for the predicted high PP trajectory group (n=50), PP increased from 44.0 mmHg at age 51 years to 67.2 mmHg at age 77 years (Figure 1). Participants in the PP trajectory groups did not differ on any demographic or health variable examined, nor on MMSE or Trails B scores (P 0.14; Table 1).

Associations between pulse pressure trajectory and brain microstructure

In base models, RI was lower in the hippocampus (β=−0.42, 95%CI=−0.74, −0.11), amygdala (β=−0.43, 95%CI=−0.75, −0.11), thalamus (β=−0.50, 95%CI=−0.84, −0.17), parahippocampal cingulum (PHC; β=−0.47, 95%CI=−0.77, −0.16), inferior longitudinal fasciculus (ILF; β=−0.42, 95%CI=−0.72, −0.11), and inferior fronto-occipital (IFO) fasciculus (β=−0.38, 95%CI=−0.67, −0.09), for those with high PP compared to low PP trajectories ($P<0.01$, Figure 2 and Table 2). Results were essentially unchanged after full adjustment (Supplemental eTable 1) or after adjustment for volume of the respective subcortical region or global white matter (Supplemental eTable 2).

APOE modifies associations between pulse pressure and brain microstructure

There were no significant interactions between PP trajectory and *APOE* status on any RSI measure at *P*<0.01, although trends for an interaction were observed for uncinate RI (*P*=0.09), IFO RI (*P*=0.08), and amygdala HI (*P*=0.06) (Supplemental eFigure 1). Because power to detect significant interactions was limited by small sample sizes, we evaluated whether differences in PP-microstructure associations were detectable when examining continuous measures of concurrent PP (Supplemental eTable 3). *APOE*-stratified partial correlations (age- and sex-adjusted) revealed significant correlations (*P*<0.01) for *APOE* ε4 carriers that were stronger than for non-carriers for RI in the hippocampus (*Z*=2.11; *P*=0.03), uncinate fasciculus (*Z*=2.38; *P*=0.02) and IFO (*Z*=2.33; *P*=0.02); and for HI in the amygdala (*Z*=2.25; *P*=0.02) (Figure 3).

Brain microstructure mediates effects of pulse pressure trajectory on executive function

Of the RSI measures that significantly (*P*<0.01) differed according to PP trajectory (Table 2), ILF RI (β=-6.94, 95%CI=-13.85, -0.03) and IFO RI (β=−8.42, 95%CI=-15.59, -1.26) were associated with lower Trails B performance in base models (Supplemental eTable 4). PP trajectory was not associated with Trails B in base (β=−7.61; SE=6.46, *P*=0.24) or fully-adjusted (β=−7.22; SE=6.20; *P*=0.23) models, however, ILF RI and IFO RI mediated the effects of PP trajectory on Trails B (ILF $\beta_a*\beta_b$=2.69, 95%CI=0.10, 7.56; IFO $\beta_a*\beta_b$=3.06, 95%CI=0.50, 8.48; Table 3). In fully-adjusted models, the mediating effect of ILF RI and IFO RI remained significant and RI in the amygdala and PHC became significantly associated with Trails B and mediated effects of PP trajectory group on Trails B (Table 3). In effect, higher PP trajectory was associated with poorer Trails B performance via reduced RI.

DISCUSSION

This study examined whether trajectories of PP over a mean 24-year follow-up predict brain microstructure in older age. A third of participants had persistently elevated and increasing PP from midlife to late-life, which predicted subcortical and white matter microstructural abnormalities. PP-microstructure associations explained impairment in Trails B test performance, which captures a range of cognitive functions that are affected by normal aging, notably executive functions, attention, and processing speed, and were modified by *APOE* genotype, with most pronounced associations for *APOE* ε4 carriers.

Our results indicating that chronically elevated and increasing PP predicts microstructural brain injury are consistent with previous cross-sectional structural and diffusion MRI studies, which reported associations between estimates of arterial stiffness and brain atrophy [39,40] or loss of gray or white matter integrity [41]. Of note, one recent study [42], reported no association between PP and the prevalence of silent brain infarcts, periventricular hyperintensities or subcortical white matter hyperintensities, or cerebral microbleeds in a sample of older Japanese adults free of dementia. However, such cross-sectional observations cannot dissociate degenerative changes reflecting an acute response to recent vascular dysfunction from accumulated damage related to worsening arterial stiffening over prolonged periods preceding MRI. Among the few studies that have assessed longitudinal changes in arterial stiffness relative to brain health in older age, findings support

the latter possibility. For instance, midlife PP and change in PP have been found to predict brain atrophy and cognitive decline 5–28 years later [16,17,40]. Notably, although midlife PP among our High PP group was within normal ranges [43], their slightly elevated levels relative to the Low PP group predicted both increased PP and microstructural injury related to poor executive function decades later. Thus, even subtle differences in midlife PP may be clinically meaningful for predicting brain aging and cognitive decline. Altogether, our results highlight the clinical utility of monitoring PP beginning in midlife to minimize the impact of chronic arterial stiffness on aging-related brain injury.

High PP was associated with reduced restricted and increased hindered diffusion within subcortical regions as well as limbic and association tracts, which may reflect neuronal loss, shrinkage, or expansion of the extracellular space. Results were unchanged after adjustment for subcortical or white matter volume and associations with free water were not observed, which would be expected in the presence of advanced atrophy, suggesting that vascular-related cytoarchitectural abnormalities were still mild in this relatively healthy sample, and perhaps amenable to therapeutic intervention. Elevated PP resulting from arterial stiffening due to aging and vascular risk factors results in a drop in mean arterial pressure and impaired arterial compliance, which can lead to transitory ischemia in the brain resulting in white matter lesions and microvascular damage due to the increased pulsatile stress that is transmitted into the cerebrovascular microcirculation [44]. Our findings suggest that this pulsatile stress may promote microscale neural injury detectable using multicompartment diffusion MRI that precedes macroscopic lesions which emerge with cerebrovascular disease.

The observed reduction in restricted diffusion in temporal regions and association fibers mediated effects of chronically elevated PP on worse executive function. These findings extend evidence from the SPRINT-MIND Study, which reported that white matter lesion volume contributed to 9.5% of executive function impairment associated with PP [20] to suggest that even subtle microstructural injury related to elevated PP has clinically significant effects on cognitive aging. The mediating regions identified here include long-range association fibers (ILF, IFO and PHC) supporting the integration of sensory and cognitive information, as well as the amygdala, which modulates efficiency of the executive control network [45]. Microstructural damage to these white matter tracts has been linked to impaired executive function in coronary artery disease [46], and amygdala atrophy has been observed in stroke/TIA patients, particularly in the presence of cognitive impairment [47]. Our results further suggest that cerebrovascular-related microstructural injury to white matter association tracts and the amygdala mediates executive function disturbance even in the absence of overt disease.

Higher PP correlated with lower restricted isotropic diffusion only among *APOE* ε4 carriers. This finding extends previous reports that *APOE* modifies associations of PP with brain atrophy, AD neuropathology, and cognitive outcomes [16–19] to demonstrate particular vulnerability of *APOE* ε4 carriers to even subtle microstructural abnormalities that may proceed advanced neurodegenerative or cognitive changes. It also adds to mounting support for a causal or modifying role of vascular dysfunction in AD pathogenesis. *APOE* ε4 carriers have a predisposition to cerebral amyloid angiopathy [48], and higher midlife PP

is associated with amyloid-β42 and phosphorylated tau [49], suggesting that exacerbation of AD pathology by arterial stiffening may be in a pivotal step in *APOE* ε4-mediated neurodegeneration.

This study had several strengths including the long-term follow-up and repeated blood pressure assessments among a well-characterized cohort of older adults, which allowed us to characterize patterns of arterial stiffness beginning midlife. Second, we used the multicompartment diffusion MRI technique RSI, which is more sensitive than conventional morphometric MRI or single-compartment diffusion MRI to nuanced brain injury that precedes gross lesions [25,26]. Several limitations should be noted. Although APOE modified associations between continuous PP and microstructure, we were limited in power to detect *APOE* differences in associations between microstructure and PP trajectory groups. The RBS cohort is comprised primarily of adults of Northern-European ancestry, and so results may not be generalizable to other populations. Although the participants included in this study were similar to those who were alive and who were invited to participate in study assessments, the analytic sample was more likely to be female and less likely to have a history of cardiovascular disease. These differences as well as the potential for selection bias common in research with older adults [50] may further limit the generalizability of our findings. Although high PP was associated with poor Trails B performance in the larger RBS cohort [23], we were likely underpowered to detect the total effect in this subsample of RBS participants; however, we observed significant mediated effects in the absence of a statistically significant total effect. As described by Rucker et al., significant mediated effects in the absence of total or direct effects may be due to power and sample size or to opposing indirect effects [51]. As we did not assess cerebrovascular perfusion or functional dynamics, future studies are needed to examine hemodynamic measures that may mediate differential effects of vascular dysfunction on brain microstructure or cognition. Subjects were screened for clinically significant cognitive impairment using the MMSE but did not undergo comprehensive neurological assessment. Thus, although mild cognitive deficits may have gone undetected, PP trajectory groups were precisely matched on cognitive status, such that any incipient cognitive impairments should be balanced between groups and not substantially influence our findings. Finally, as we relied on PP as a surrogate marker of arterial stiffness [52], which may result in exposure misclassification, validation is needed with studies measuring pulse pressure using assessments that meet current recommendations [53]. However, because PP is highly predictive of cardiovascular risk and arterial stiffness is a primary determinant of PP [54], any discrepancy between PP and arterial stiffness measures should not meaningfully alter the interpretation of our findings.

CONCLUSIONS

Among older adults free of dementia, prolonged elevated PP predicts subcortical and white matter microstructural abnormalities, particularly for those at risk for dementia, and may contribute to impaired executive function via microstructural injury. Monitoring PP beginning in midlife, even among those with slight abnormalities, may be a cost-effective and readily accessible approach to minimize the impact of arterial stiffening on brain health and reduce the risk of cognitive decline. Our findings underscore the importance of considering one's genetic profile for personalized risk assessment and for guiding

targeted therapeutic interventions, as well as the need for further investigation into additional demographic or lifestyle factors that may modify effects of vascular dysfunction on brain aging trajectories.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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RESEARCH IN CONTEXT

1. Systematic Review: The authors reviewed the published peer-reviewed literature using traditional sources. The effects of pulse pressure (PP) on cognition and brain health have been previously examined in cross-sectional structural and diffusion MRI studies. The effects of chronic arterial stiffness on neurobiological aging, however, have been understudied. These relevant studies were appropriately cited.

2. Interpretation: Consistent with findings in the public domain, we hypothesized that long-term elevated PP predicts brain microstructure and that microstructure mediates PP-executive function associations.

3. Future Directions: We propose that pulsatile stress may promote microscale neural injury that precedes macroscopic lesions which emerge with cerebrovascular disease, and that monitoring PP may be a cost-effective approach to minimize the impact of arterial stiffening on brain health and reduce the risk of cognitive decline. Intervention studies that test these hypotheses will be critical to understanding the impact of chronic elevated PP on brain health.
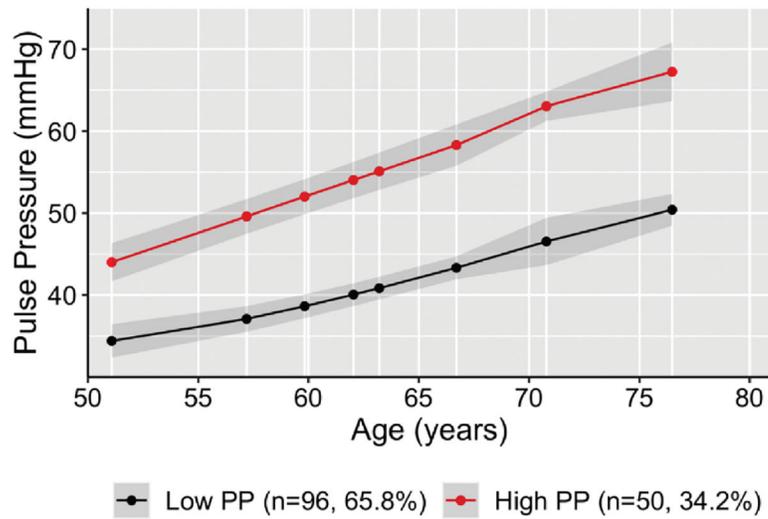
Figure 1. Predicted pulse pressure (PP) trajectories (Low PP or High PP).
PP trajectories were classified using latent class growth modeling based on a maximum of eight pulse pressure measurements made from 1984 to 2016 among the 146 Rancho Bernardo Study participants.
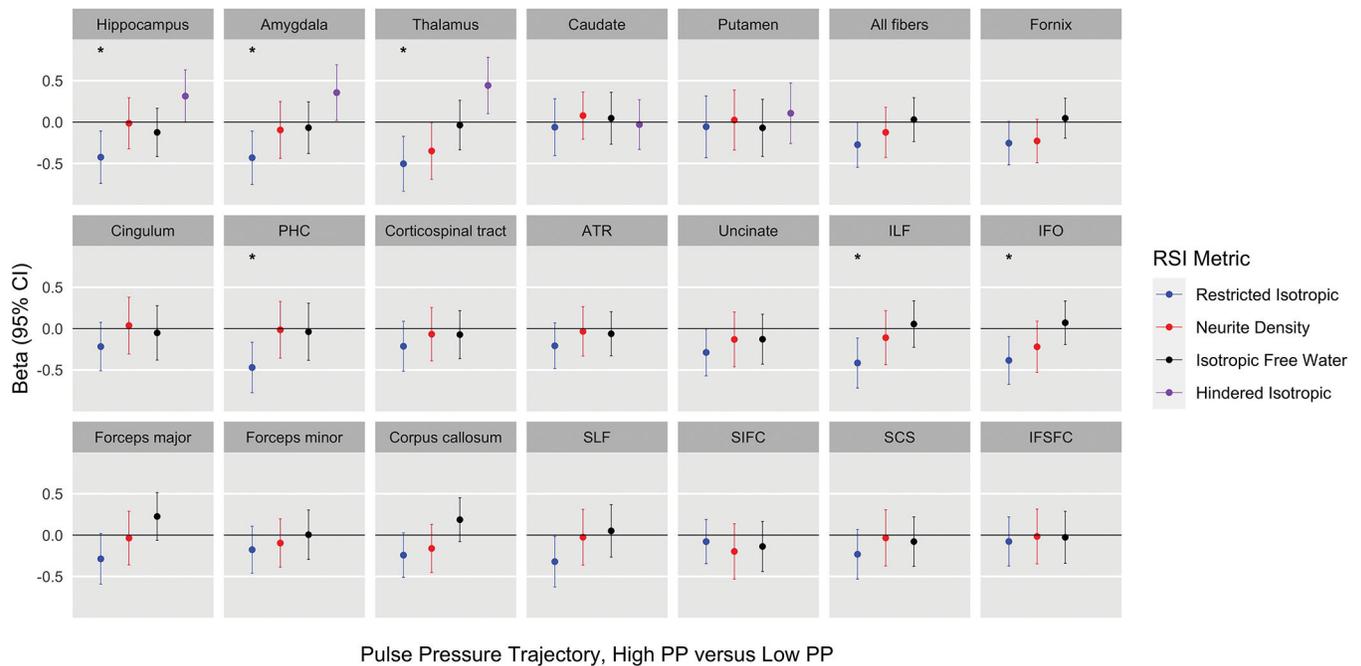
Figure 2. Differences in RSI metrics by pulse pressure (PP) trajectory group.
Beta estimates and 95% confidence intervals (CIs) are shown for the difference in standardized RSI metrics [restricted isotropic (blue), neurite density (red), isotropic free water (black), and hindered isotropic (purple)] between High PP (*n*=50) versus Low PP (*n*=96) trajectory groups from multiple linear regression models adjusted for age (continuous, years) and sex (male or female). Abbreviations: ATR, anterior thalamic radiation; ILF, inferior longitudinal fasciculus; IFO, inferior fronto-occipital fasciculus; PHC, parahippocampal cingulum; SLF, superior longitudinal fasciculus; SIFC, striatal inferior frontal cortex; SCS, superior corticostriate; IFSFC, inferior-frontal superior-frontal cortex. *P<0.01

Hippocampus

r = −0.17; *P* = 0.08
r = −0.55; *P* < 0.01
z = 2.11; *P* = 0.03

ε4 carriers
ε4 non-carriers

Uncinate fasciculus

r = −0.15; *P* = 0.12
r = −0.58; *P* < 0.01
z = 2.38; *P* = 0.02

ε4 carriers
ε4 non-carriers

Inferior fronto-occipital fasciculus

r = −0.13; *P* = 0.21
r = −0.55; *P* < 0.01
z = 2.33; *P* = 0.02

ε4 carriers
ε4 non-carriers

Amygdala

r = 0.15; *P* = 0.13
r = 0.55; *P* < 0.01
z = 2.25; *P* = 0.02

ε4 non-carriers
ε4 carriers
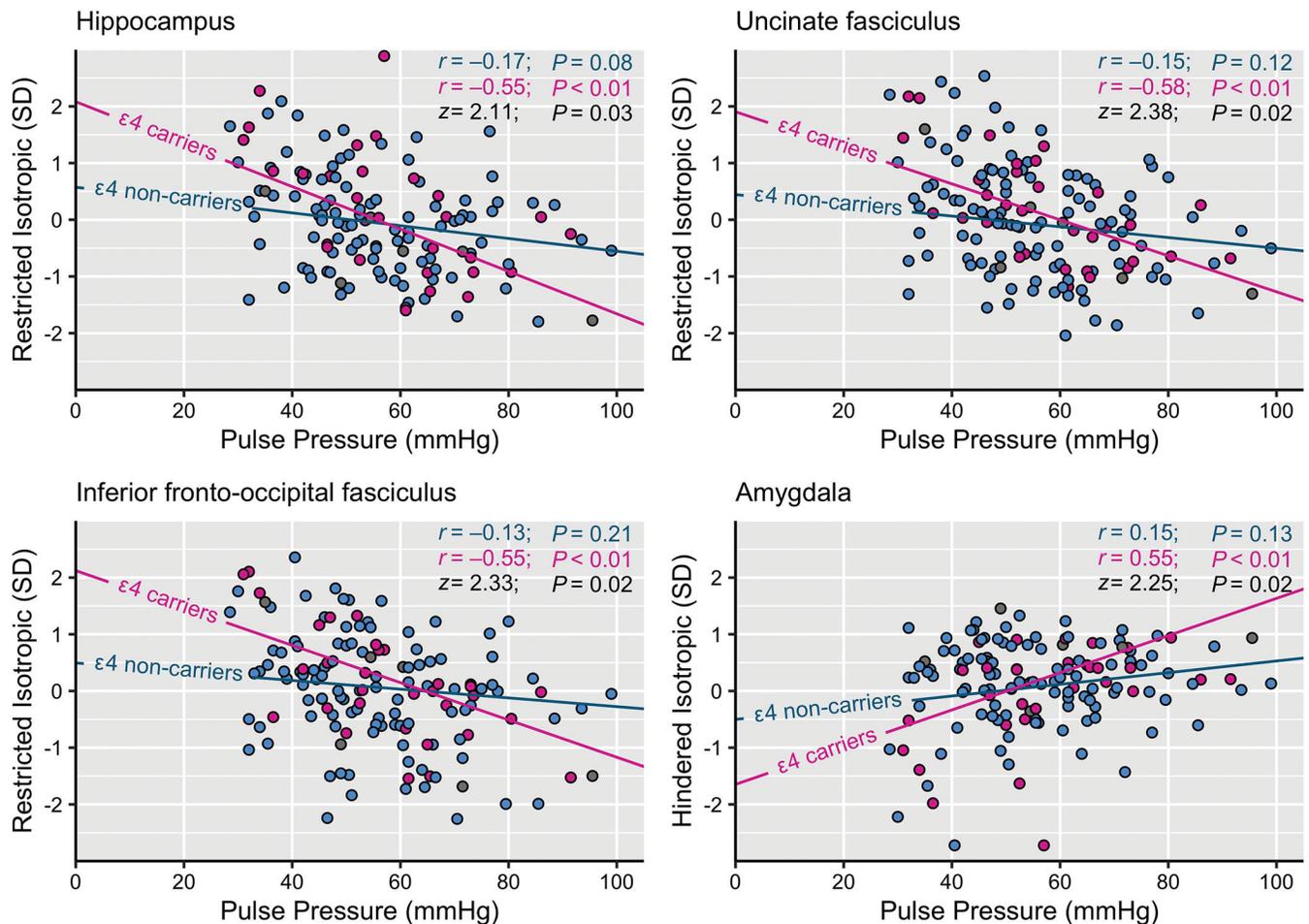
Figure 3. Differences in associations between pulse pressure and microstructure by *APOE* ε4 status.

Partial correlations (*r*, adjusted for age and sex) between cross-sectional pulse pressure and RSI metrics (per standard deviation [SD] increase), stratified by *APOE* ε4 status, are shown for subcortical regions and fiber tracts in which correlations differed by *APOE* ε4 status [ε4 non-carriers (blue), *n*=106; ε4 carriers, *n*=32 (magenta)]. Note: Regression lines were computed at mean-centered age = 0 and sex = female.

Table 1.

Characteristics of Rancho Bernardo Study participants in 2014-2016 (n=221) and the analytic sample included in this study (n=146) overall and by pulse pressure trajectory group.

Characteristic	Overall	Low PP (n=96)	High PP (n=50)	P^a
	Latent Class Assignment of Pulse Pressure (PP) Trajectory			
	n (%)	n (%)	n (%)	
Age (years), mean (SD)	76.6 (7.8)	75.9 (8.2)	78.0 (7.1)	0.14
Sex				
Female	90 (61.6)	57 (59.4)	33 (66.0)	
Male	56 (38.4)	39 (49.6)	17 (34.0)	0.44
Education (years), mean (SD)	14.9 (2.1)	15.0 (2.2)	14.7 (1.9)	0.48
Alcohol consumption in the past year				
Non-drinker	21 (14.5)	12 (12.6)	9 (18.0)	
Drinker	124 (85.5)	83 (87.4)	41 (82.0)	0.38
1 or more times per week	93 (75.0)	60 (72.3)	33 (80.5)	
Less than 1 time per week	31 (25.0)	23 (27.7)	8 (19.5)	
Missing	1	1	0	
Smoking status				
Never smoker	85 (58.6)	56 (59.0)	29 (58.0)	
Former or current smoker	60 (41.4)	39 (41.0)	21 (42.0)	0.91
Missing	1	1	0	
Exercise, 3 times per week				
No	35 (24.1)	22 (23.2)	13 (26.0)	
Yes	110 (75.9)	73 (76.8)	37 (74.0)	0.70
Missing	1	1	0	
Body mass index (kg/m^2), mean (SD)	26.0 (4.0)	25.6 (3.9)	26.5 (4.1)	0.22
Missing	4	4	0	
History of cardiovascular disease				
No	128 (87.7)	86 (88.6)	42 (84.0)	
Yes	18 (12.3)	10 (10.4)	8 (16.0)	0.33
History of diabetes				
No	131 (89.7)	85 (88.5)	46 (92.0)	
Yes	15 (10.3)	11 (11.5)	4 (8.0)	0.51
APOE ε4				
ε4 non-carriers	106 (76.8)	68 (76.4)	38 (77.6)	
ε4 carriers	32 (23.2)	21 (23.6)	11 (22.4)	0.88
Missing	8	7	1	
MMSE, mean (SD)	28.9 (1.3)	28.9 (1.3)	28.9 (1.3)	0.98
Trails B (seconds), mean (SD)	87.2 (41.1)	88.4 (46.1)	84.6 (28.8)	0.60

[a]P-values from independent samples t-tests for continuous covariates or χ^2 tests for categorical covariates.

Table 2.

Beta (β) estimates and 95% confidence intervals (CIs) from age- and sex-adjusted multiple linear regression models for associations between latent class assignment of pulse pressure (PP) trajectory (High PP versus Low PP) and RSI metrics in subcortical regions and fiber tracts (*n*=146).

Region	Restricted Isotropic β (95% CI)[a]	P	Neurite Density β (95% CI)[a]	P	Isotropic Free Water β (95% CI)[a]	P	Hindered Isotropic β (95% CI)[a]	P
Subcortical								
Hippocampus	−0.42 (−0.74, −0.11)	<0.01*	−0.01 (−0.32, 0.29)	0.93	−0.12 (−0.42, 0.17)	0.40	0.31 (0, 0.63)	0.05
Amygdala	−0.43 (−0.75, −0.11)	<0.01*	−0.10 (−0.44, 0.25)	0.58	−0.07 (−0.38, 0.24)	0.67	0.36 (0.02, 0.69)	0.04
Thalamus	−0.50 (−0.84, −0.17)	<0.01*	−0.35 (−0.69, −0.01)	0.05	−0.04 (−0.34, 0.26)	0.81	0.44 (0.1, 0.78)	0.01
Caudate	−0.06 (−0.41, 0.28)	0.72	0.08 (−0.21, 0.36)	0.59	0.05 (−0.27, 0.36)	0.77	−0.03 (−0.33, 0.27)	0.85
Putamen	−0.06 (−0.43, 0.32)	0.77	0.02 (−0.34, 0.39)	0.89	−0.07 (−0.41, 0.28)	0.69	0.11 (−0.26, 0.47)	0.56
Fibers								
All fibers	−0.27 (−0.55, 0.00)	0.05	−0.12 (−0.43, 0.18)	0.42	0.03 (−0.24, 0.3)	0.82		
Fornix	−0.25 (−0.52, 0.01)	0.06	−0.23 (−0.49, 0.03)	0.09	0.05 (−0.19, 0.29)	0.70		
Cingulum	−0.22 (−0.51, 0.08)	0.14	0.04 (−0.31, 0.38)	0.83	−0.05 (−0.38, 0.28)	0.76		
Parahippocampal cingulum	−0.47 (−0.77, −0.16)	<0.01*	−0.01 (−0.36, 0.33)	0.93	−0.04 (−0.38, 0.31)	0.83		
Corticospinal tract	−0.21 (−0.52, 0.09)	0.16	−0.07 (−0.39, 0.26)	0.68	−0.07 (−0.36, 0.22)	0.62		
Anterior thalamic radiation	−0.21 (−0.48, 0.07)	0.14	−0.03 (−0.33, 0.26)	0.82	−0.06 (−0.33, 0.20)	0.64		
Uncinate fasciculus	−0.29 (−0.57, −0.01)	0.05	−0.13 (−0.46, 0.20)	0.44	−0.13 (−0.43, 0.17)	0.40		
Inferior longitudinal fasciculus	−0.42 (−0.72, −0.11)	<0.01*	−0.11 (−0.44, 0.22)	0.51	0.06 (−0.23, 0.34)	0.70		
Inferior fronto-occipital fasciculus	−0.38 (−0.67, −0.09)	<0.01*	−0.22 (−0.53, 0.09)	0.16	0.07 (−0.19, 0.33)	0.60		
Forceps major	−0.29 (−0.59, 0.02)	0.07	−0.04 (−0.36, 0.29)	0.83	0.23 (−0.06, 0.51)	0.12		
Forceps minor	−0.18 (−0.46, 0.11)	0.22	−0.10 (−0.39, 0.20)	0.52	0.00 (−0.29, 0.30)	0.98		
Corpus callosum	−0.24 (−0.51, 0.03)	0.08	−0.16 (−0.45, 0.13)	0.27	0.19 (−0.08, 0.45)	0.17		
Superior longitudinal fasciculus	−0.32 (−0.63, −0.01)	0.04	−0.03 (−0.36, 0.31)	0.88	0.05 (−0.27, 0.37)	0.75		
Striatal inferior frontal cortex	−0.08 (−0.35, 0.19)	0.56	−0.20 (−0.53, 0.14)	0.25	−0.14 (−0.44, 0.17)	0.37		
Superior corticostriate	−0.23 (−0.53, 0.07)	0.13	−0.03 (−0.37, 0.31)	0.85	−0.08 (−0.38, 0.22)	0.60		
Inferior-frontal superior-frontal cortex	−0.08 (−0.37, 0.22)	0.61	−0.02 (−0.35, 0.31)	0.92	−0.03 (−0.34, 0.29)	0.87		

[a] Model is adjusted for age (continuous, years) and sex (male or female).

*
$P<0.01$

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Table 3.

Results from single mediation analyses showing significant mediation of pulse pressure (PP) trajectory on Trails B performance by microstructure (n=146).

	a-pathway	b-pathway	a*b-pathway
	β_a (SE)	β_b	$\beta_a*\beta_b$ (95% CI)
Amygdala (RI)			
Base Model[a]	−0.43 (0.17)	−4.52 (3.32)	1.94 (−1.42, 7.29)
Fully-Adjusted Model[b]	−0.43 (0.16)	−9.66 (3.32)	4.13 (0.91, 11.01)
Parahippocampal cingulum (RI)			
Base Model[a]	−0.46 (0.16)	−4.76 (3.47)	2.21 (−0.89, 6.81)
Fully-Adjusted Model[b]	−0.45 (0.16)	−8.35 (3.46)	3.77 (0.95, 9.93)
Inferior longitudinal fasciculus			
Base Model[a]	−0.39 (0.15)	−6.94 (3.49)	2.69 (0.10, 7.56)
Fully-Adjusted Model[b]	−0.38 (0.16)	−8.18 (3.48)	3.12 (0.53, 8.73)
Inferior fronto-occipital fasciculus (RI)			
Base Model[a]	−0.36 (0.15)	−8.42 (3.62)	3.06 (0.50, 8.48)
Fully-Adjusted Model[b]	−0.39 (0.15)	−9.10 (3.68)	3.59 (0.51, 10.21)

[a] Model is adjusted for age (continuous, years) and sex (male or female),

[a] Model is adjusted for age (continuous, years), sex (male or female), education (continuous, years), alcohol consumption (non-drinker or drinker), body mass index (continuous, kg/m^2), history of cardiovascular disease (no or yes), *APOE* ε4 (ε4 non-carrier or ε4 carrier), pulse pressure trajectory group (high PP vs. low PP), and RSI measure (continuous, 1-SD unit), as appropriate.

The a-pathway reflects the effect of PP group on RSI, the b-pathway reflects the effect of RSI on Trails B, and the a*b-pathway indicates the indirect effect of PP group on Trails B via RSI (mediation).