Visit-to-visit Blood Pressure Variability and Regional Cerebral Perfusion Decline in Older Adults

Isabel Sible
University of Southern California https://orcid.org/0000-0003-3922-0628
Belinda Yew
University of Southern California
Shubir Dutt
University of Southern California
Katherine J. Bangen
University of California San Diego
Yanrong Li
University of California Irvine
Daniel A. Nation (dnation@uci.edu)
University of California Irvine

Research

Keywords: blood pressure variability, cerebral perfusion, Alzheimer's disease, aging

Posted Date: December 17th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-129456/v1

Abstract

Background: Blood pressure variability has been linked to dementia risk, independent of average blood pressure levels. It has been hypothesized that dysregulated blood pressure may challenge autoregulatory mechanisms and risk cerebral hypoperfusion. The current study examined whether visit-to-visit blood pressure variability over one year is related to concurrent regional cerebral perfusion decline over the same period in older adults.

Methods: Sixty-three older adults without history of dementia or stroke underwent repeated blood pressure measurement and arterial spin-labelling magnetic resonance imaging over the same one year period. Fluorodeoxyglucose-positron emission tomography determined cerebral metabolism at baseline. A subset underwent lumbar puncture to detect cerebral spinal fluid amyloid-beta (n=18) and phosphorylated tau (n=21) abnormalities. Visit-to-visit blood pressure variability and change in regional cerebral perfusion were both calculated over 12 months. Multiple linear regression examined relationships between blood pressure variability and change in regional perfusion after controlling for age, sex, average blood pressure, antihypertensive medication use and cerebral metabolism. Exploratory analyses were repeated in participant subsets with abnormal cerebral spinal fluid amyloid-beta and phosphorylated tau.

Results: Elevated blood pressure variability was related to perfusion decline in medial orbitofrontal cortex (ß = -.36; p = .008), hippocampus (ß = -.37; p = .005), entorhinal cortex (ß = -.48; p < .001), precuneus (ß = -.31; p = .02), inferior parietal cortex (ß = -.44; p < .001) and inferior temporal cortex (ß = -.46; p < .001). Elevated blood pressure variability was similarly related to perfusion decline in some regions among participant subsets showing abnormal cerebral spinal fluid amyloid-beta and phosphorylated tau.

Conclusions: Older adults with elevated visit-to-visit blood pressure variability exhibit concurrent regional cerebral perfusion decline in areas vulnerable to cerebrovascular dysfunction in Alzheimer's disease, independent of cerebral hypometabolism. Similar findings are observed in exploratory analyses of older adults with Alzheimer's disease biomarker abnormalities. The study is limited by the small sample size, particularly the subset of participants with Alzheimer's disease biomarker abnormalities. Findings may have therapeutic implications, given that certain antihypertensive medications have differential effects on variability of blood pressure independent of average levels.

Introduction

Vascular factors in cognitive decline and dementia are increasingly appreciated.[1] Both high and low blood pressure (BP) and reduced cerebral blood flow (CBF) are related to Alzheimer's disease (AD) pathology and predictive of cognitive decline with progression to AD dementia.[2–6] Beyond average BP, there is growing interest in visit-to-visit (e.g., months and years) blood pressure variability (BPV) in the context of cognitive impairment and dementia. Recent studies link visit-to-visit BPV to dementia risk, including AD and vascular dementia, independent of and beyond average BP levels,[7–17] even in older

adults with well controlled average BP.[18] Visit-to-visit BPV elevation appears to occur before the onset of major neurocognitive dysfunction and in the context of AD pathophysiology,[19] suggesting a possible early marker of vascular dysfunction in the aging process. Although mechanisms linking increased BPV to AD remain understudied, it has been hypothesized that inflated BPV may alter processes both highly dependent on BP and critical for cognition, such as cerebral perfusion.[8, 9, 15, 17] Over time, chronic BP oscillation may stress arterial walls and promote microvascular damage, leading to blood-brain barrier breakdown and subsequent neuronal damage.[8, 9, 15, 17] These fluctuations in BP may challenge cerebral autoregulation and risk cerebral hypoperfusion injury,[7–9, 17] an effect that may particularly involve brain regions already vulnerable to hypoperfusion in AD.[7–9, 17, 20] Alternatively, neurodegeneration of cortical autonomic centers may increase BPV, accounting for an association between BPV and dementia risk.[8, 21] To address these possibilities, we studied older adults over a one year period to determine whether BPV is related to cerebral perfusion decline over time, independent of baseline cerebral metabolism.

Methods

Participants

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database.[22] The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), and other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. Adults aged 55–91 were recruited from several sites across North America and were enrolled if they met the following criteria: few depressive symptoms (Geriatric Depression Scale < 6), free of history of neurological disease (other than suspected AD), no greater than mild dementia symptoms (Clinical Dementia Rating scale < = 1), and low vascular risk (Hachinski Ischemic Score < = 4). More detailed descriptions of ADNI recruitment and enrollment criteria are described on the ADNI site (https://adni.loni.usc.edu).

The present study included participants who underwent clinical evaluation and fluorodeoxyglucose (FDG)-PET at study baseline and BP measurement at study screening, baseline, and 6- and 12- months follow-up. Participants also underwent repeated arterial spin-labelling (ASL)-MRI at study baseline and 12-months follow-up. A subset of participants underwent lumbar puncture to determine cerebral spinal fluid (CSF) AD biomarker levels.

Measures

Clinical assessment

Baseline clinical evaluation identified participants as cognitively normal or MCI without history of dementia or stroke.[22] Criteria for a diagnosis of MCI included: subjective memory complaint reported by

the participant or informant; Mini Mental State Exam scores between 24 and 30 (inclusive); global Clinical Dementia Rating scale score of 0.5; scores on delayed recall of Story A of the Wechsler Memory Scale Revised Logical Memory II subtest that are below expected performance based on years of education; general presentation that would disqualify for a diagnosis of AD.[23] Participants were categorized as cognitively normal (CN) if MCI diagnostic criteria were not met. CN and MCI participants then were collapsed into one category of older adults free of dementia and used in all analyses.

CSF AD biomarker assessment

Baseline lumbar puncture and CSF analysis in a subset of participants determined amyloid-beta (Aβ) and phosphorylated tau (Ptau) levels as described elsewhere.[24–27] Using established guidelines, CSF Aβ levels ≤ 980 pg/mL and CSF Ptau levels ≥ 21.8 pg/mL were considered abnormal.[26, 28]

BP assessment

Qualified medical professionals obtained BP measurements from participants at study screening, baseline, and 6- and 12-months follow-up using a calibrated mercury sphygmomanometer. Participants were seated comfortably and resting, encouraged to refrain from talking during and shortly before BP measurement, and to remain as calm and undisturbed as possible. Measurement was taken from the dominant arm, with the forearm at the horizontal level of the fourth intercostal space at the sternum. BP was taken from the same arm, at a similar time of day, by the same person, and using the same device and cuff, whenever possible.[22]

The main index of intraindividual BPV was calculated using the four BP measurements over the 12 month period as variation independent of mean (VIM), a commonly used index of visit-to-visit BPV that is uncorrelated with average BP.[9, 14, 19, 29] VIM was calculated as:

$$VIM = \text{standard deviation}/\text{mean}^{x}$$

where the power x was derived from non-linear curve fitting of BP standard deviation (SD) against average BP using the nls package in R Project,[30] as described elsewhere.[29] Intraindividual BPV was also calculated as the SD and coefficient of variation (CV [100 × SD/mean]) using the four BP measurements.

Regional CBF change assessment

CBF was determined from pulsed ASL-MRI at study screening and 12 months follow-up for several regions-of-interest previously identified as vulnerable to cerebrovascular dysfunction in AD:[3, 4] medial orbitofrontal cortex (mOFC), hippocampus, posterior cingulate, entorhinal cortex, precuneus, inferior parietal cortex (IPC), rostral middle frontal gyrus (rMFG), and inferior temporal cortex (ITC). CBF values were residualized by precentral gyrus CBF, a region relatively spared in AD and consistent with previous studies of ASL-MRI using the ADNI dataset.[3, 4] CBF values were then averaged bilaterally. Change in CBF was calculated as the difference between regional CBF at screening and 12-months follow-up and used in all analyses.

Cerebral metabolism assessment

Glucose uptake from regions linked to metabolic dysfunction in AD was determined from baseline FDG-PET to index cerebral metabolism as previously described.[4]

STATISTICAL ANALYSES

Primary analysis included the total sample of 63 older adults available in ADNI who had valid ASL-MRI at study screening and 12 months follow-up, four valid BP measurements over the same 12 month period and were without history of dementia or stroke. Exploratory analysis included the subset of participants with AD biomarker abnormalities (18 participants with Aβ abnormality and 21 participants with Ptau abnormality). Demographic and clinical descriptive data (means and SDs) are shown in Table 1. BPV values were log-transformed to approach a normal distribution. Multiple linear regression examined relationships between BPV using VIM measure of variability and regional CBF change. All analyses controlled for age, sex, average BP, and cerebral metabolism. Primary analyses also controlled for use of antihypertensive medication. Supplementary analyses examined relationships using SD and CV measures of variability (See Supplementary Materials). Based on a power analysis for detecting moderate-to-large effect sizes using G*Power,[31] multiple linear regression (α = .05, 5 covariates) with a sample size of 56 older adults will yield 95% power. As such, the current study is adequately powered to detect moderate-to-large effect sizes in primary analyses. All analyses were 2-tailed with significance at $p < .05$. False Discovery Rate (FDR) was set at $p < .05$.[32] Reported values for multiple linear regression include: standardized beta (ß), *p*-value (*p*), and partial eta-squared (η_p^2) with 95% confidence interval. All analyses were carried out in R Project.[30]

Results

In the primary analysis total sample, elevated systolic BPV was related to decline in CBF in mOFC (ß = − .36; $p = .008$; $\eta_p^2 = .11$ [95% .01, .28]), hippocampus (ß = − .37; $p = .005$; $\eta_p^2 = .12$ [.01, .29]), entorhinal cortex (ß = − .48; $p < .001$; $\eta_p^2 = .20$ [.05, .38]), precuneus (ß = − .31; $p = .02$; $\eta_p^2 = .07$ [.00, .22]), IPC (ß = − .44; $p < .001$; $\eta_p^2 = .19$ [.04, .37]) and ITC (ß = − .46; $p < .001$; $\eta_p^2 = .17$ [.02, .35]), but findings did not reach statistical significance in posterior cingulate or rMFG (all *p's* > .11) (Fig. 1). Increased diastolic BPV was related to decline in CBF in mOFC (ß = − .38; $p = .009$; $\eta_p^2 = .08$ [.00, .24]), hippocampus (ß = − .51; $p < .001$; $\eta_p^2 = .20$ [.05, .38]), entorhinal cortex (ß = − .45; $p = .002$; $\eta_p^2 = .14$ [.01, .31]), precuneus (ß = − .42; $p = .003$; $\eta_p^2 = .09$ [.00, .25]), posterior cingulate (ß = − .38; $p = .008$; $\eta_p^2 = .09$ [.00, .26]), IPC (ß = − .32; $p = .03$; $\eta_p^2 = .05$ [.00, .20]) and ITC (ß = − .40; $p = .008$; $\eta_p^2 = .10$ [.00, .27]), but findings did not reach statistical significance in rMFG ($p = .15$) (Data not shown).

After FDR correction, systolic BPV findings remained significant for all regions in the primary analysis total sample.

Analyses using SD and CV indices of variability showed similar relationships with regional CBF change in the primary analysis total sample (see Supplementary Results).

Among participants with Aβ abnormality in the exploratory analysis, increased systolic BPV was related to decline in CBF in mOFC (ß = − .59; p = .008; η_p^2 = .55 [95% .12, .76]), entorhinal cortex (ß = − .50; p = .03; η_p^2 = .42 [.03, .69]), precuneus (ß = − .55; p = .03; η_p^2 = .36 [.00, .65]), IPC (ß = − .73; p < .001; η_p^2 = .79 [.48, .89]) and ITC (ß = − .48; p = .03; η_p^2 = .44 [.02, .72]), but findings did not reach statistical significance in hippocampus, posterior cingulate or rMFG (all p's > .10) **(**Fig. 2**)**. Elevated diastolic BPV was related to decline in CBF in hippocampus (ß = − .58; p = .02; η_p^2 = .40 [.02, .68) and entorhinal cortex (ß = − .60; p = .009; η_p^2 = .49 [.07, .73), but findings did not reach statistical significance in mOFC, posterior cingulate, precuneus, IPC, ITC or rMFG (all p's > .07) (Data not shown).

Among participants with Ptau abnormality in the exploratory analysis, elevated systolic BPV was related to decline in CBF in mOFC (ß = − .57; p = .02; η_p^2 = .38 [95% .03, .64]), hippocampus (ß = − .65; p = .002; η_p^2 = .53 [.15, .74]), entorhinal cortex (ß = − .46; p = .04; η_p^2 = .39 [.04, .65]), precuneus (ß = − .53; p = .02; η_p^2 = .39 [.04, .65]), IPC (ß = − .60; p = .001; η_p^2 = .66 [.32, .82]) and ITC (ß = − .62; p = .01; η_p^2 = .48 [.06, .73]), but findings did not reach statistical significance in posterior cingulate or rMFG (all p's > .25) **(**Fig. 3**).** Elevated diastolic BPV was related to decline in CBF in hippocampus (ß = − .62; p = .02; η_p^2 = .36 [.03, .63]) but findings did not reach statistical significance in mOFC, entorhinal cortex, posterior cingulate, precuneus, IPC, ITC or rMFG (all p's > .06) (Data not shown).

After FDR correction, systolic BPV findings remained significant for all regions in participants with Aβ biomarker abnormality in the exploratory analysis, and for all regions except entorhinal cortex (p = .053) in participants with Ptau biomarker abnormality in the exploratory analysis using VIM index of variability.

Analyses using SD and CV indices of variability showed similar relationships with regional CBF change in participants with AD biomarker abnormality in exploratory analysis (see Supplementary Results). Findings similarly survived FDR correction using SD and CV indices of variability (see Supplementary Results) in exploratory analysis.

Discussion

Findings indicate elevated visit-to-visit BPV is related to concurrent cerebral perfusion decline over time in regions susceptible to AD pathophysiology, independent of cerebral hypometabolism. This pattern of regional cerebral perfusion decline was also observed in exploratory analysis of older adults with AD biomarker abnormalities based on CSF Aβ and Ptau levels. Results support the hypothesized link between increased BPV and CBF compromise, which may underpin increased risk for dementia associated with elevated BPV.[7–9, 12] Increased BPV may represent an understudied aspect of vascular dysfunction in aging, with potential diagnostic and treatment implications.

Increased BPV is also associated with white matter hyperintensities, cerebral microbleeds and increased risk for stroke.[7, 33] Present study findings suggest BPV is related to perfusion decline in regions associated with cerebrovascular dysfunction in AD[4] even in a sample with limited cerebrovascular disease (e.g., Hachinski score ≤ 4). Future work should explore potential interactions between BPV, microvascular injury and CBF in older adults with and without cognitive impairment and cerebrovascular disease.

A study strength is the longitudinal design of both BPV and CBF measures obtained over the same period. Although causal inference is still limited even for longitudinal studies, our results are consistent with a potential effect of BPV on susceptibility to cerebral hypoperfusion injury. Alternatively, neurodegeneration could impact both regional cerebral perfusion and BPV through effects on cortical autonomic centers.[21] However, findings were independent of cerebral metabolism, suggesting BPV may influence cerebral perfusion through a vascular mechanism.

Limitations

The current study is limited by the small sample size, particularly in the CSF AD biomarker exploratory analysis. As such, interpretation of findings from the exploratory analysis is limited. However, primary analyses were adequately powered to detect moderate-to-large effect sizes according to a power analysis using G*Power.[31] Nevertheless, findings indicate increased BPV is associated with decline in CBF over time in older adults with AD biomarker abnormality, potentially implicating BPV in CBF changes observed in AD patients. Importantly, study participants were cognitively unimpaired or MCI, suggesting the potential influence of BPV on CBF is an early event that precedes major cognitive dysfunction. The current study examined all participants free of dementia due to sample size limitations. Future studies should evaluate the timeline of BPV changes linked to cerebral perfusion decline in older adults with normal cognition and MCI. Another study limitation is that data were collected from several sites (n = 14). Although two studies on BPV using ADNI data included BP measurements from several study sites out of the potential 50 + sites contributing to ADNI,[19, 34] limiting the number of sites for data collection may lower measurement error. Additionally, the study sample was largely comprised of non-Hispanic White older adults with limited cerebrovascular disease. Some evidence suggests that the relationship between cerebrovascular disease and cognitive impairment may differ by ethnicity.[35] Therefore, generalizability of study findings to other racial and ethnic groups is limited. Finally, although the present study could not address potential class effects of antihypertensive treatment on BPV, various antihypertensive medications have differential effects on BPV,[36] independent of mean BP, suggesting there may be clinical implications for studies of BPV in AD.

Conclusions

Findings indicate older adults with elevated visit-to-visit BPV exhibit concurrent cerebral perfusion decline in AD vulnerable regions over the same one year period, a finding that remained in those with AD

biomarker abnormality, independent of cerebral hypometabolism. Increased BPV may convey susceptibility to dementia through links with cerebral hypoperfusion injury.

Abbreviations

BP = blood pressure; BPV = blood pressure variability; CBF = cerebral blood flow; AD = Alzheimer's disease; CSF = cerebral spinal fluid; ADNI = Alzheimer's Disease Neuroimaging Initiative; MRI = magnetic resonance imaging; PET = positron emission tomography; MCI = mild cognitive impairment; FDG-PET = fluorodeoxyglucose positron emission tomography; ASL-MRI = arterial spin-labelling magnetic resonance imaging; CN = cognitively normal; Aβ = amyloid-beta; Ptau = phosphorylated tau; VIM = variation independent of mean; SD = standard deviation; CV = coefficient of variation; mOFC = medial orbitofrontal cortex; IPC = inferior parietal cortex; rMFG = rostral middle frontal gyrus; ITC = inferior temporal cortex; FDR = False Discovery Rate; ß = standardized beta; p = p-value; η_p^2 = partial eta-squared

Declarations

Ethics Approval and Consent to Participate

The study was approved by each institution and all participants provided written informed consent prior to study enrollment.

Consent for Publication

Not applicable.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are available in the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, https://adni.loni.usc.edu.

Competing Interests

The authors declare that they have no competing interests.

Funding

The study data analysis was supported by NIH/NIA grants (R01AG064228, R01AG060049, R21AG055034, P50 AG005142, and P01 AG052350), NSF grant DGE1418060 and Alzheimer's Association grant AARG-17-532905. Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery

Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

Authors' Contributions

IJS designed the study, analyzed and interpreted the data and prepared the manuscript; BY contributed to the study design and revised the manuscript; SB revised the manuscript; KJB revised the manuscript; YL revised the manuscript; DAN contributed to the study design and data analysis and data interpretation and revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements

None.

References

1. Zlokovic B V. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. Nat Rev Neurosci. Nature Publishing Group; 2011;12:723–38.
2. Wolters FJ, Zonneveld HI, Hofman A, Van Der Lugt A, Koudstaal PJ, Vernooij MW, et al. Cerebral perfusion and the risk of dementia: A population-based study. Circulation. 2017;136:719–28.
3. Mattsson N, Tosun D, Insel PS, Simonson A, Jack CR, Beckett LA, et al. Association of brain amyloid-β with cerebral perfusion and structure in Alzheimer's disease and mild cognitive impairment. Brain. 2014;137:1550–61.
4. Yew B, Nation DA. Cerebrovascular resistance: Effects on cognitive decline, cortical atrophy, and progression to dementia. Brain. 2017;140:1987–2001.
5. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. Lancet Neurol. 2005;4:487–99.
6. Lane CA, Barnes J, Nicholas JM, Sudre CH, Cash DM, Parker TD, et al. Associations between blood pressure across adulthood and late-life brain structure and pathology in the neuroscience substudy of the 1946 British birth cohort (Insight 46): an epidemiological study. Lancet Neurol [Internet]. The

Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license; 2019;18:942–52. Available from: http://dx.doi.org/10.1016/S1474-4422(19)30228-5

7. Yoo JE, Shin DW, Han K, Kim D, Lee SP, Jeong SM, et al. Blood pressure variability and the risk of dementia: a nationwide cohort study. Hypertension. 2020;75:982–90.
8. Lattanzi S, Vernieri F, Silvestrini M. Blood pressure variability and neurocognitive functioning. J Clin Hypertens. 2018;20:645–7.
9. Rouch L, Cestac P, Sallerin B, Piccoli M, Benattar-Zibi L, Bertin P, et al. Visit-to-visit blood pressure variability is associated with cognitive decline and incident dementia: The S.AGES cohort. Hypertension. 2020;76:1280–8.
10. Lattanzi S, Luzzi S, Provinciali L, Silvestrini M. Blood pressure variability predicts cognitive decline in Alzheimer's disease patients. Neurobiol Aging [Internet]. Elsevier Ltd; 2014;35:2282–7. Available from: http://dx.doi.org/10.1016/j.neurobiolaging.2014.04.023
11. Lattanzi S, Viticchi G, Falsetti L, Buratti L, Luzzi S, Provinciali L, et al. Visit-to-visit blood pressure variability in Alzheimer disease. Alzheimer Dis Assoc Disord. 2014;28:347–51.
12. Ma Y, Wolters FJ, Chibnik LB, Licher S, Ikram MA, Hofman A, et al. Variation in blood pressure and long-term risk of dementia : A population-based cohort study. PLoS Med [Internet]. 2019;16:1–16. Available from: http://dx.doi.org/10.1371/journal.pmed.1002933
13. Alpérovitch A, Blachier M, Soumaré A, Ritchie K, Dartigues JF, Richard-Harston S, et al. Blood pressure variability and risk of dementia in an elderly cohort, the Three-City Study. Alzheimer's Dement. 2014;10:S330–7.
14. de Heus RAA, Olde Rikkert MGM, Tully PJ, Lawlor BA, Claassen JAHR. Blood pressure variability and progression of clinical Alzheimer disease. Hypertension. 2019;74:1172–80.
15. Oishi E, Ohara T, Sakata S, Fukuhara M, Hata J, Yoshida D, et al. Day-to-day blood pressure variability and risk of dementia in a general Japanese elderly population: The Hisayama study. Circulation. 2017;136:516–25.
16. Qin B, Viera AJ, Muntner P, Plassman BL, Edwards LJ, Adair LS, et al. Visit-to-visit variability in blood pressure is related to late-life cognitive decline. Hypertension. 2016;68:106–13.
17. Nagai M, Dote K, Kato M, Sasaki S, Oda N, Kagawa E, et al. Visit-to-visit blood pressure variability and Alzheimer's disease: Links and risks. J Alzheimer's Dis. 2017;59:515–26.
18. Cho N, Hoshide S, Nishizawa M, Fujiwara T, Kario K. Relationship Between Blood Pressure Variability and Cognitive Function in Elderly Patients With Good Blood Pressure Control. Am J Hypertens. 2018;31:293–8.
19. Sible IJ, Nation DA, Alzheimer's Disease Neuroimaging Initiative. Long-term blood pressure variability across the clinical and biomarker spectrum of Alzheimer's disease. J Alzheimer's Dis [Internet]. 2020;77:1655–69. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32925032
20. Iadecola C. Neurovascular regulation in the normal brain and in Alzheimer's disease. Nat Rev Neurosci. 2004;5:347–60.

21. Nagai M, Hoshide S, Kario K. The insular cortex and cardiovascular system: a new insight into the brain-heart axis. J Am Soc Hypertens. 2010;4:174–82.
22. Alzheimer's Disease Neuroimaging Initiative [Internet]. 2017. Available from: http://adni.loni.usc.edu/
23. Petersen RC, Aisen PS, Beckett LA, Donohue MC, Gamst AC, Harvey DJ, et al. Alzheimer's Disease Neuroimaging Initiative (ADNI): Clinical characterization. Neurology. 2010;74:201–9.
24. Shaw LM, Fields L, Korecka M, Waligórska T, Trojanowski JQ, Allegranza D, et al. Method comparison of AB(1-42) measured in human cerebrospinal fluid samples by liquid chromatography-tandem mass spectrometry, the INNO-BIA AlzBio3 assay, and the Elecsys® B-Amyloid(1-42) assay. Alzheimer's Dement. 2016;12:P668.
25. Bittner T, Zetterberg H, Teunissen CE, Ostlund RE, Militello M, Andreasson U, et al. Technical performance of a novel, fully automated electrochemiluminescence immunoassay for the quantitation of β-amyloid (1-42) in human cerebrospinal fluid. Alzheimer's Dement. 2016;
26. Hansson O, Seibyl J, Stomrud E, Zetterberg H, Trojanowski JQ, Bittner T, et al. CSF biomarkers of Alzheimer's disease concord with amyloid-β PET and predict clinical progression: A study of fully automated immunoassays in BioFINDER and ADNI cohorts. Alzheimer's Dement. 2018;14:1470–81.
27. Seibyl J, Shaw LM, Blennow K, Widmann M, Corradini V, Wahl S, et al. Amyloid-PET concordance of Elecsys® CSF biomarker immunoassays for Alzheimer's disease. Alzheimer's Dement [Internet]. Elsevier; 2017;13:P199–200. Available from: http://dx.doi.org/10.1016/j.jalz.2017.07.062
28. Shaw LM, Waligorska T, Fields L, Korecka M, Figurski M, Trojanowski JQ, et al. Derivation of cutoffs for the Elecsys® amyloid β (1–42) assay in Alzheimer's disease. Alzheimer's Dement Diagnosis, Assess Dis Monit [Internet]. Elsevier Inc.; 2018;10:698–705. Available from: https://doi.org/10.1016/j.dadm.2018.07.002
29. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet [Internet]. Elsevier Ltd; 2010;375:895–905. Available from: http://dx.doi.org/10.1016/S0140-6736(10)60308-X
30. R Core Team. R: A language and environment for statistical computing. 2018.
31. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. Behav Res Methods. 2009;41:1149–60.
32. Benjamini Y, Hochberg Y. Controlling the false discovery rate: A practical and powerful approach to multiple testing. R Stat Soc. 1995;
33. Brickman AM, Reitz C, Luchsinger JA, Manly JJ, Schupf N, Muraskin J, et al. Long-term blood pressure fluctuation and cerebrovascular disease in an elderly cohort. Arch Neurol. 2010;67:564–9.
34. Epstein NU, Lane KA, Farlow MR, Risacher SL, Saykin AJ, Gao S. Cognitive dysfunction and greater visit-to-visit systolic blood pressure variability. J Am Geriatr Soc. 2013;61:2168–73.
35. Johnson LA, Cushing B, Rohlfing G, Edwards M, Davenloo H, D'Agostino D, et al. The Hachinski Ischemic Scale and cognition: The influence of ethnicity. Age Ageing. 2014;43:364–9.

36. Webb AJ, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: A systematic review and meta-analysis. Lancet [Internet]. Elsevier Ltd; 2010;375:906–15. Available from: http://dx.doi.org/10.1016/S0140-6736(10)60235-8

Table

Table 1.

Baseline clinical and demographic data

	Total sample (N = 63)	**Aβ abnormality (n = 18)**	**Ptau abnormality (n = 21)**
Age (years)	70.5 (7.0)	72.4 (7.2)	72.8 (7.3)
Sex (M/F)	27 / 36	7 / 11	7 / 14
Education (years)	16.8 (2.5)	16.7 (2.9)	16.5 (2.8)
APOE-ϵ4 carriers (n,%)	17 (27.0%)	6 (33.3%)	6 (28.6%)
MMSE score	27.5 (4.4)	24.5 (7.5)	25.1 (7.0)
Diagnosis (% MCI)	65.1%	61.1%	52.4%
BMI (kg/m^2)	26.6 (3.5)	25.2 (2.8)	26.3 (3.3)
Antihypertensive use (n,%)	25 (39.7%)	8 (44.4%)	9 (42.9%)
Systolic BP (mmHg)	132.5 (14.4)	133.6 (14.6)	135.4 (16.0)
Diastolic BP (mmHg)	73.1 (7.1)	74.3 (5.8)	74.1 (6.0)
Systolic BPV (mmHg)	8.2 (4.4)	8.7 (4.3)	8.5 (4.2)
Diastolic BPV (mmHg)	3.7 (2.8)	3.9 (3.2)	4.6 (3.4)
Cerebral metabolism (SUV)	1.3 (0.1)	1.2 (0.1)	1.2 (0.1)
CSF Aβ (pg/mL)	–	761.2 (153.0)	776.4 (182.9)
CSF Ptau (pg/mL)	–	30.5 (15.9)	33.1 (12.8)
Means and standard deviations shown unless otherwise indicated.			
Abbreviations: M = male; F = female; MMSE = Mini Mental State Exam; BP = blood pressure; BPV = blood pressure variability; BMI = body mass index; MCI = Mild Cognitive Impairment; SUV = standardized uptake value; CSF = cerebral spinal fluid; Aβ = amyloid-beta; Ptau = phosphorylated tau			

Figures

Figure 2.

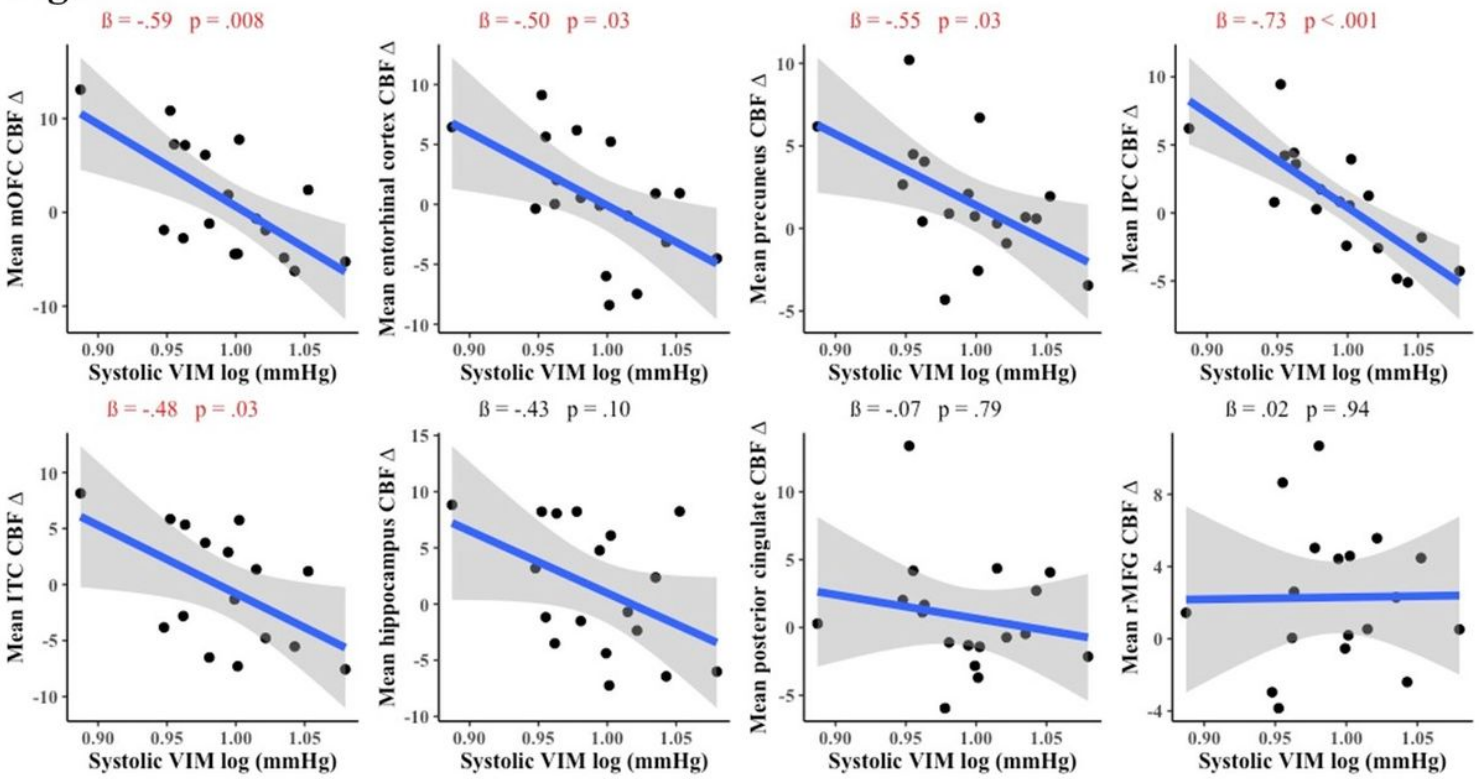

Figure 1

Elevated systolic BPV is linked to regional CBF decline in older adults with Aβ abnormality Scatterplots display the results of the linear regression between systolic BPV using VIM measure of variability and regional CBF change (mL/100g/min) over 12 months in older adults with Aβ abnormality. 95% confidence interval is shaded around the regression lines. Abbreviations: BPV = blood pressure variability; CBF = cerebral blood flow; mOFC = medial orbitofrontal cortex; IPC = inferior parietal cortex; ITC = inferior temporal cortex; rMFG = rostral middle frontal gyrus; Aβ = amyloid-beta

Figure 3.

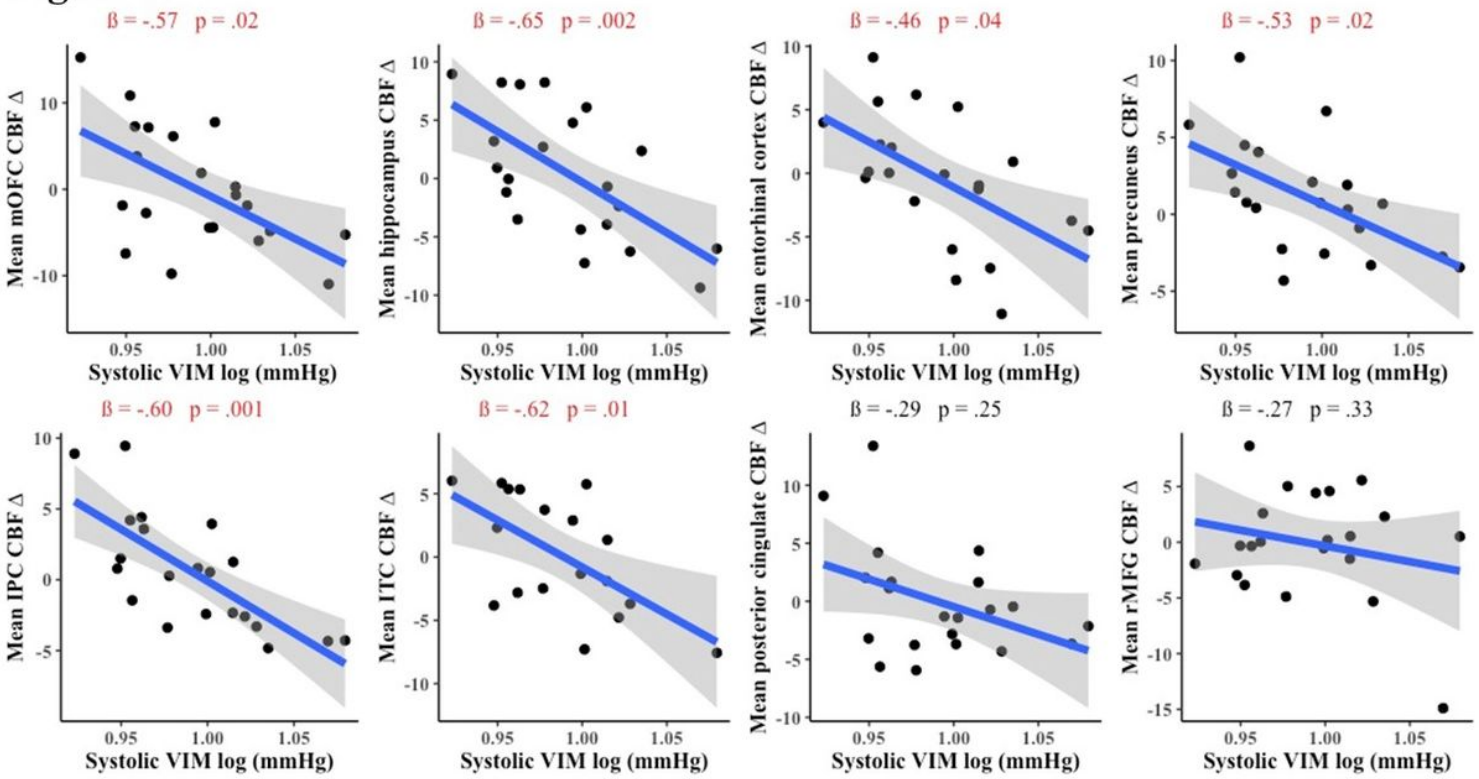

Figure 1

Elevated systolic BPV is linked to regional CBF decline in older adults with Ptau abnormality Scatterplots display the results of the linear regression between systolic BPV using VIM measure of variability and regional CBF change (mL/100g/min) over 12 months in older adults with Ptau abnormality. 95% confidence interval is shaded around the regression lines. Abbreviations: BPV = blood pressure variability; CBF = cerebral blood flow; mOFC = medial orbitofrontal cortex; IPC = inferior parietal cortex; ITC = inferior temporal cortex; rMFG = rostral middle frontal gyrus; Ptau = phosphorylated tau

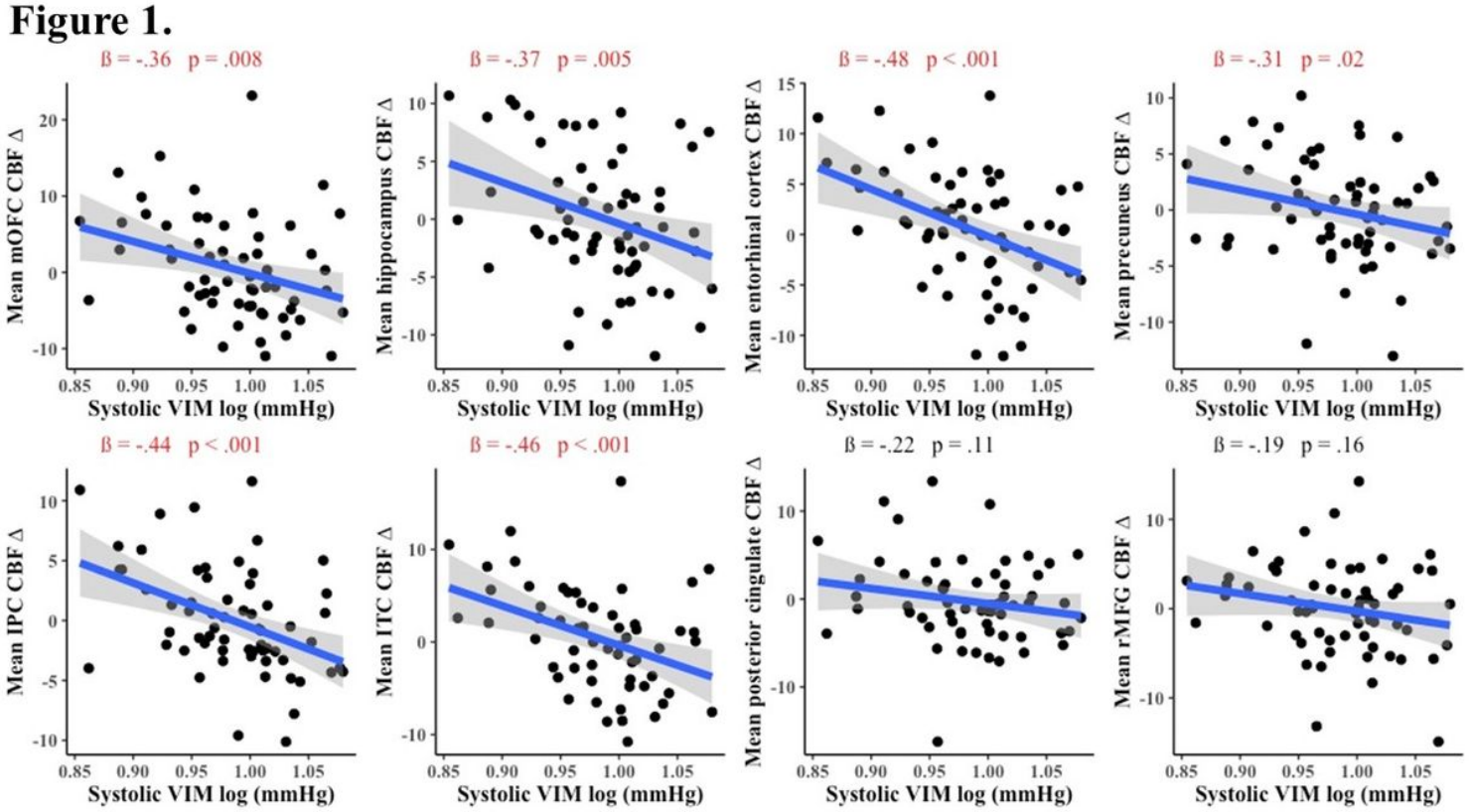

Figure 1

Elevated systolic BPV is related to regional CBF decline in older adults without dementia Scatterplots display the results of the linear regression between systolic BPV using VIM measure of variability and regional CBF change (mL/100g/min) over 12 months in older adults without dementia. 95% confidence interval is shaded around the regression lines. Abbreviations: BPV = blood pressure variability; CBF = cerebral blood flow; mOFC = medial orbitofrontal cortex; IPC = inferior parietal cortex; ITC = inferior temporal cortex; rMFG = rostral middle frontal gyrus

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SUPPLEMENTARYMATERIAL.docx