Title

Visit-to-visit blood pressure variability and regional cerebral perfusion decline in older adults

Authors

Sible, Isabel J
Yew, Belinda
Dutt, Shubir
et al.

Publication Date

2021-09-01

DOI

10.1016/j.neurobiolaging.2021.04.009

Peer reviewed

HHS Public Access

Author manuscript

Neurobiol Aging. Author manuscript; available in PMC 2022 April 04.

Published in final edited form as:

Neurobiol Aging. 2021 September ; 105: 57–63. doi:10.1016/j.neurobiolaging.2021.04.009.

Visit-to-visit blood pressure variability and regional cerebral perfusion decline in older adults

Isabel J. Sible, MA[a], **Belinda Yew, PhD**[a], **Shubir Dutt, MA**[a,b], **Katherine J. Bangen, PhD**[c,d], **Yanrong Li, BA**[e], **Daniel A. Nation, PhD**[e,f,#], **Alzheimer's Disease Neuroimaging Initiative**[*]

[a]Department of Psychology, University of Southern California, Los Angeles, CA 90007, USA

[b]Davis School of Gerontology, University of Southern California, Los Angeles, CA 90007, USA

[c]Research Service, Veteran Affairs San Diego Health Care System, San Diego, CA 92161, USA

[d]Department of Psychiatry, University of California, San Diego, La Jolla, CA 92093, USA

[e]Institute for Memory Impairments and Neurological Disorders, University of California, Irvine, Irvine, CA 92697, USA

[f]Department of Psychological Science, University of California, Irvine, Irvine, CA 92697, USA

Abstract

Blood pressure variability (BPV) is linked to dementia risk, possibly through cerebral hypoperfusion. We investigated BPV over 1 year and concurrent regional cerebral perfusion decline in older adults without dementia. Participants underwent 4 blood pressure measurements across 12 months, ASL-MRI at baseline and 12-months, and baseline FDG-PET. Regional perfusion was normalized to precentral gyrus. A subset had cerebral spinal fluid Alzheimer's disease biomarker abnormalities. For every SD increase in BPV, perfusion decreased in medial orbitofrontal cortex (ß = −.36; $p = 0.008$), hippocampus (ß = −.37; $p = 0.005$), entorhinal cortex (ß = −.48; $p < 0.001$), precuneus (ß = −.31; $p = 0.02$), inferior parietal cortex (ß = −.44; $p < 0.001$), and inferior temporal cortex (ß = −.46; $p < 0.001$). Similar patterns emerged in subsets with biomarker abnormalities. Older adults with elevated BPV exhibit concurrent regional perfusion decline in areas vulnerable to Alzheimer's disease, independent of cerebral hypometabolism. BPV may be an early marker of vascular dysfunction in aging.

Keywords

blood pressure variability; cerebral perfusion; Alzheimer's disease; aging

[#]Corresponding Author: Daniel A. Nation, Ph.D., Associate Professor, University of California Irvine, Department of Psychological Science, Institute for Memory Impairments and Neurological Disorders, 4201 Social and Behavioral Sciences Gateway, Irvine, CA 92697-7085, Phone: (949) 824-9339, Fax: (949) 824-3002, dnation@uci.edu.

[*]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

DECLARATIONS OF INTEREST

None.

1. INTRODUCTION

Vascular factors in cognitive decline and dementia are increasingly appreciated (Zlokovic, 2011). 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 (Lane et al., 2019; Mattsson et al., 2014; Qiu et al., 2005; Wolters et al., 2017; Yew and Nation, 2017). 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 (Alpérovitch et al., 2014; de Heus et al., 2019; Lattanzi et al., 2018; Ma et al., 2019; Nagai et al., 2017; Oishi et al., 2017; Qin et al., 2016; Rouch et al., 2020; Yoo et al., 2020), even in older adults with well controlled average BP (Cho et al., 2018). Visit-to-visit BPV elevation appears to occur before the onset of major neurocognitive dysfunction and in the context of AD pathophysiology (Sible et al., 2020), 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 (Lattanzi et al., 2018; Nagai et al., 2017; Oishi et al., 2017; Rouch et al., 2020). Over time, chronic BP oscillation may stress arterial walls and promote microvascular damage, leading to blood-brain barrier breakdown and subsequent neuronal damage (Lattanzi et al., 2018; Nagai et al., 2017; Oishi et al., 2017; Rouch et al., 2020). These fluctuations in BP may challenge cerebral autoregulation and risk cerebral hypoperfusion injury (Lattanzi et al., 2018; Nagai et al., 2017; Rouch et al., 2020; Yoo et al., 2020), an effect that may particularly involve brain regions already vulnerable to hypoperfusion in AD (Iadecola, 2004; Lattanzi et al., 2018; Nagai et al., 2017; Rouch et al., 2020; Yoo et al., 2020). Alternatively, neurodegeneration of cortical autonomic centers may increase BPV, accounting for an association between BPV and dementia risk (Lattanzi et al., 2018; Nagai et al., 2010). To address these possibilities, we studied older adults over a 1-year period to determine whether BPV is related to cerebral perfusion decline over time, independent of baseline cerebral metabolism.

2. METHODS

2.1 Participants

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database ("Alzheimer's Disease Neuroimaging Initiative," 2017). 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. Volunteer adults aged 55–91, with or without memory complaints, were recruited through several sites at Alzheimer's Disease Research Centers and other academic medical institutions across North America via newsletters, internet-based communications, direct mail, and

news releases. Participants 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 63 participants who underwent clinical evaluation and fluorodeoxyglucose (FDG)-PET at study baseline, BP measurement at study screening, baseline, and 6- and 12- months follow-up, and repeated arterial spin-labelling (ASL)-MRI at study baseline and 12-months follow-up. A subset of participants underwent lumbar puncture to determine abnormal cerebral spinal fluid (CSF) AD biomarker levels of amyloid-beta (Aβ) (n = 18) and phosphorylated tau (Ptau) (n = 21) (see Supplementary Figure 1).

2.1.1 Standard protocol approvals, registration, and patient consents—

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

2.2 Measures

2.2.1 Clinical assessment—

Baseline clinical evaluation identified participants as cognitively normal or MCI without history of dementia or stroke ("Alzheimer's Disease Neuroimaging Initiative," 2017). Criteria for a diagnosis of MCI included: subjective memory complaint reported by the participant or informant; Mini Mental State Exam (MMSE) 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 (Petersen et al., 2010). Participants were categorized as cognitively normal if MCI diagnostic criteria were not met. Cognitively normal and MCI participants then were collapsed into 1 category of older adults free of dementia and used in all analyses.

2.2.2 CSF AD biomarker assessment—

Baseline lumbar puncture and CSF analysis in a subset of participants determined Aβ and Ptau levels as described elsewhere (Bittner et al., 2016; Hansson et al., 2018; Seibyl et al., 2017; Shaw et al., 2016). Using established guidelines, CSF Aβ levels ≤ 980 pg/mL and CSF Ptau levels ≥ 21.8 pg/mL were considered abnormal (Hansson et al., 2018; Shaw et al., 2018).

2.2.3 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 ("Alzheimer's Disease Neuroimaging Initiative," 2017). The main index of intraindividual BPV was calculated using the 4 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 (de Heus et al., 2019; Rothwell et al., 2010; Rouch et al., 2020; Sible et al., 2020). VIM was calculated as: VIM = standard deviation/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 (R Core Team, 2018), as described elsewhere (Rothwell et al., 2010). Intraindividual BPV was also calculated as the SD and coefficient of variation (CV [100 x SD/mean]) using the 4 BP measurements.

2.2.4 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 (Mattsson et al., 2014; Yew and Nation, 2017): medial orbitofrontal cortex (mOFC), hippocampus, posterior cingulate, entorhinal cortex, precuneus, inferior parietal cortex (IPC), rostral middle frontal gyrus (rMFG), and inferior temporal cortex (ITC). To adjust for individual variation in flow, 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 (Mattsson et al., 2014; Yew and Nation, 2017). Briefly, regional CBF values were regressed onto precentral gyrus CBF and resulting residual values were extracted. 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.

2.2.5 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 (Yew and Nation, 2017).

2.2.6 Whole brain gray matter volume and white matter hyperintensity assessment—Baseline total gray matter volume across the whole brain and white matter hyperintensities were determined from baseline MRI using methods described elsewhere ("Alzheimer's Disease Neuroimaging Initiative," 2017).

2.2.7 Data availability statement—The datasets generated and/or analyzed during the current study are available in the ADNI database, https://adni.loni.usc.edu.

2.3 Statistical analysis

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. Primary analyses investigated relationships in the total sample of older adults without history of dementia or stroke. Exploratory analyses examined relationships in participant subsets with AD biomarker abnormality. All analyses controlled for age, sex, average BP, and cerebral metabolism. Primary analyses also controlled for use of antihypertensive medication at baseline. Supplementary analyses examined relationships using SD and CV measures of variability, as well as with average BP over the 12-month

period (see Supplementary Materials). Based on a power analysis for detecting moderate-to-large effect sizes using G*Power (Faul et al., 2009), multiple linear regression ($\alpha = .05$, 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. Additional analyses were performed to test the robustness of primary findings by substituting baseline cerebral metabolism, to preserve statistical power, with: 1) baseline whole brain gray matter volume; 2) baseline CBF in each corresponding ROI; 3) baseline white matter hyperintensities; and 4) baseline MMSE. All analyses were 2-tailed with significance at $p < 0.05$. False Discovery Rate (FDR) was set at $p < 0.05$ (Benjamini and Hochberg, 1995). 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 (R Core Team, 2018).

3. RESULTS

Demographic and clinical descriptive data (means and SDs) are shown in Table 1.

In the primary analysis total sample, elevated systolic BPV was related to decline in CBF in mOFC (ß = −.36; $p = 0.008$; $\eta_p^2 = .11$ [95% .01, .28]), hippocampus (ß = −.37; $p = 0.005$; $\eta_p^2 = .12$ [.01, .29]), entorhinal cortex (ß = −.48; $p < 0.001$; $\eta_p^2 = .20$ [.05, .38]), precuneus (ß = −.31; $p = 0.02$; $\eta_p^2 = .07$ [.00, .22]), IPC (ß = −.44; $p < 0.001$; $\eta_p^2 = .19$ [.04, .37]) and ITC (ß = −.46; $p < 0.001$; $\eta_p^2 = .17$ [.02, .35]), but findings did not reach statistical significance in posterior cingulate or rMFG (all *p's* > 0.11) (Figure 1). Increased diastolic BPV was related to decline in CBF in mOFC (ß = −.38; $p = 0.009$; $\eta_p^2 = .08$ [.00, .24]), hippocampus (ß = −.51; $p < 0.001$; $\eta_p^2 = .20$ [.05, .38]), entorhinal cortex (ß = −.45; $p = 0.002$; $\eta_p^2 = .14$ [.01, .31]), precuneus (ß = −.42; $p = 0.003$; $\eta_p^2 = .09$ [.00, .25]), posterior cingulate (ß = −.38; $p = 0.008$; $\eta_p^2 = .09$ [.00, .26]), IPC (ß = −.32; $p = 0.03$; $\eta_p^2 = .05$ [.00, .20]) and ITC (ß = −.40; $p = 0.008$; $\eta_p^2 = .10$ [.00, .27]), but findings did not reach statistical significance in rMFG ($p = 0.15$) (Data not shown).

After FDR correction, systolic and diastolic BPV findings remained significant for all regions in the primary analysis total sample. See Supplementary Table 1 for FDR-corrected *p*-values (i.e., *q*-values).

Analyses using SD and CV indices of variability showed similar relationships with regional CBF change in the primary analysis total sample (see Supplementary Results). No significant relationships were observed between average BP and CBF change for any ROI in the primary analysis total sample (*p*'s = .09 to .99) (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; $p = 0.008$; $\eta_p^2 = .55$ [95% .12, .76]), entorhinal cortex (ß = −.50; $p = 0.03$; $\eta_p^2 = .42$ [.03, .69]), precuneus (ß = −.55; $p = 0.03$; $\eta_p^2 = .36$ [.00, .65]), IPC (ß = −.73; $p < 0.001$; $\eta_p^2 = .79$ [.48, .89]) and ITC (ß = −.48; $p = 0.03$; $\eta_p^2 = .44$ [.02, .72]), but findings did not reach statistical significance in hippocampus, posterior cingulate or rMFG (all *p*'s > 0.10) (Figure 2). Elevated diastolic BPV was related to decline in CBF in hippocampus (ß = −.58; $p = 0.02$; $\eta_p^2 = .40$ [.02, .68]) and entorhinal

cortex (ß = −.60; $p = 0.009$; $\eta_p^2 = .49$ [.07, .73]), but findings did not reach statistical significance in mOFC, posterior cingulate, precuneus, IPC, ITC or rMFG (all p's > 0.07) (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; $p = 0.02$; $\eta_p^2 = .38$ [95% .03, .64]), hippocampus (ß = −.65; $p = 0.002$; $\eta_p^2 = .53$ [.15, .74]), entorhinal cortex (ß = −.46; $p = 0.04$; $\eta_p^2 = .39$ [.04, .65]), precuneus (ß = −.53; $p = 0.02$; $\eta_p^2 = .39$ [.04, .65]), IPC (ß = −.60; $p = 0.001$; $\eta_p^2 = .66$ [.32, .82]) and ITC (ß = −.62; $p = 0.01$; $\eta_p^2 = .48$ [.06, .73]), but findings did not reach statistical significance in posterior cingulate or rMFG (all p's > 0.25) (Figure 3). Elevated diastolic BPV was related to decline in CBF in hippocampus (ß = −.62; $p = 0.02$; $\eta_p^2 = .36$ [.03, .63]) but findings did not reach statistical significance in mOFC, entorhinal cortex, posterior cingulate, precuneus, IPC, ITC or rMFG (all p's > 0.06) (Data not shown).

After FDR correction of exploratory analyses in participants with Aβ biomarker abnormality, systolic BPV findings remained significant for all regions and diastolic BPV findings in the hippocampus ($q = .08$) and entorhinal cortex ($q = .07$) were no longer significant. After FDR correction of exploratory analyses in participants with Ptau biomarker abnormality, systolic BPV findings remained significant for all regions except entorhinal cortex ($q = .053$), and the diastolic BPV finding in the hippocampus was no longer significant ($q = .16$). See Supplementary Table 1 for FDR-corrected p-values (i.e., q-values).

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 in exploratory analysis (see Supplementary Results).

Sensitivity analyses revealed essentially the same primary results when controlling for baseline whole brain gray matter volume, baseline CBF for each ROI, baseline white matter hyperintensities, and baseline MMSE (see Supplementary Results).

4. 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 (Lattanzi et al., 2018; Ma et al., 2019; Rouch et al., 2020; Yoo et al., 2020). 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 (Brickman et al., 2010; Yoo et al., 2020). Present study findings

suggest BPV is related to perfusion decline in regions associated with cerebrovascular dysfunction in AD (Yew and Nation, 2017) even in a sample with limited cerebrovascular disease (e.g., Hachinski score ≤ 4). Sensitivity analyses revealed study findings to be largely unchanged when controlling for baseline white matter hyperintensities, although the sample notably had minimal white matter hyperintensity burden. Additionally, ASL-MRI only provides reliable perfusion estimates for gray matter structures, limiting any conclusions regarding relationships with white matter pathology. Future work should explore potential interactions between BPV, microvascular injury and CBF in older adults with and without cognitive impairment and varying levels of cerebrovascular disease burden.

A study strength is the use of longitudinal BPV and CBF data. However, both longitudinal measurements were collected over the same period, limiting interpretation of the temporal order of findings. However, our cross-sectional findings 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 (Nagai et al., 2010). However, findings were independent of cerebral metabolism and whole brain gray matter volume, suggesting BPV may influence cerebral perfusion through a vascular mechanism. Dynamic autoregulatory functions governing the relationship between BP changes and CBF have been well studied by transcranial doppler (Aaslid et al., 1989). However, transcranial doppler is limited to measuring blood flow velocity through larger intracranial arteries (D'Andrea et al., 2016). The present study adds to our understanding of the relationship between BP change and CBF by utilizing ASL-MRI to assess BPV in relation to regional tissue perfusion decline in areas with known importance in cognition and AD.

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 (Faul et al., 2009). 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, and primary findings were essentially unchanged when controlling for baseline MMSE score, suggesting the relationship between BPV and CBF decline is not due to a spurious association with major neurocognitive 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. Relatedly, ASL-MRI was obtained only from a subset of participants enrolled in a particular wave of the overall ADNI study, and those with longitudinal ASL-MRI at study baseline and 12-months follow-up represent an even smaller sample. Fortunately, 100% of these participants had 4 BP measurements collected over the same time period. Despite the completeness of the BP data within this ADNI participant subset, there is always the possibility of selection bias. While several methods are available to assess relative change in CBF, we chose to residualize regional CBF values by precentral gyrus CBF to be consistent with the methods in 2 other ASL-MRI studies using the ADNI dataset (Mattsson et al., 2014; Yew and Nation, 2017). Another study limitation is that

data were collected from several sites (n= 14). Although 2 studies on BPV using ADNI data included BP measurements from several study sites out of the potential 50+ sites contributing to ADNI (Epstein et al., 2013; Sible et al., 2020), 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 (Johnson et al., 2014). Therefore, generalizability of study findings to other racial and ethnic groups is limited. While the current investigation took into account antihypertensive medication use at baseline, we were not able to address the potential influence of treatment initiation or discontinuation. Finally, although the present study could not address potential class effects of antihypertensive treatment on BPV, various antihypertensive medications have differential effects on BPV (Webb et al., 2010), independent of mean BP, suggesting there may be clinical implications for studies of BPV in AD.

5. CONCLUSIONS

Findings indicate older adults with elevated visit-to-visit BPV exhibit concurrent cerebral perfusion decline in AD vulnerable regions over the same 1-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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

SOURCES OF 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.

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

REFERENCES

Aaslid R, Lindegaard KF, Sorteberg W, Nornes H, 1989. Cerebral autoregulation dynamics in humans. Stroke 20, 45–52. 10.1161/01.STR.20.1.45 [PubMed: 2492126]

Alpérovitch A, Blachier M, Soumaré A, Ritchie K, Dartigues JF, Richard-Harston S, Tzourio C, 2014. Blood pressure variability and risk of dementia in an elderly cohort, the Three-City Study. Alzheimer's Dement 10, S330–S337. 10.1016/j.jalz.2013.05.1777 [PubMed: 23954028]

Alzheimer's Disease Neuroimaging Initiative [WWW Document], 2017. URL http://adni.loni.usc.edu/

Benjamini Y, Hochberg Y, 1995. Controlling the false discovery rate: A practical and powerful approach to multiple testing. R. Stat. Soc 57, 289–300.

Bittner T, Zetterberg H, Teunissen CE, Ostlund RE, Militello M, Andreasson U, Hubeek I, Gibson D, Chu DC, Eichenlaub U, Heiss P, Kobold U, Leinenbach A, Madin K, Manuilova E, Rabe C, Blennow K, 2016. Technical performance of a novel, fully automated electrochemiluminescence

immunoassay for the quantitation of β-amyloid (1–42) in human cerebrospinal fluid. Alzheimer's Dement 10.1016/j.jalz.2015.09.009

Brickman AM, Reitz C, Luchsinger JA, Manly JJ, Schupf N, Muraskin J, DeCarli C, Brown TR, Mayeux R, 2010. Long-term blood pressure fluctuation and cerebrovascular disease in an elderly cohort. Arch. Neurol 67, 564–569. 10.1001/archneurol.2010.70 [PubMed: 20457955]

Cho N, Hoshide S, Nishizawa M, Fujiwara T, Kario K, 2018. Relationship Between Blood Pressure Variability and Cognitive Function in Elderly Patients With Good Blood Pressure Control. Am. J. Hypertens 31, 293–298. 10.1093/ajh/hpx155 [PubMed: 28985341]

D'Andrea A, Conte M, Cavallaro M, Scarafile R, Riegler L, Cocchia R, Pezzullo E, Carbone A, Natale F, Santoro G, Caso P, Russo MG, Bossone E, Calabrò R, 2016. Transcranial Doppler ultrasonography: From methodology to major clinical applications. World J. Cardiol 8, 383. 10.4330/wjc.v8.i7.383 [PubMed: 27468332]

de Heus RAA, Olde Rikkert MGM, Tully PJ, Lawlor BA, Claassen JAHR, 2019. Blood pressure variability and progression of clinical Alzheimer disease. Hypertension 74, 1172–1180. 10.1161/HYPERTENSIONAHA.119.13664 [PubMed: 31542965]

Epstein NU, Lane KA, Farlow MR, Risacher SL, Saykin AJ, Gao S, 2013. Cognitive dysfunction and greater visit-to-visit systolic blood pressure variability. J. Am. Geriatr. Soc 61, 2168–2173. 10.1111/jgs.12542 [PubMed: 24479146]

Faul F, Erdfelder E, Buchner A, Lang AG, 2009. Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. Behav. Res. Methods 41, 1149–1160. 10.3758/BRM.41.4.1149 [PubMed: 19897823]

Hansson O, Seibyl J, Stomrud E, Zetterberg H, Trojanowski JQ, Bittner T, Lifke V, Corradini V, Eichenlaub U, Batrla R, Buck K, Zink K, Rabe C, Blennow K, Shaw LM, 2018. 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 14, 1470–1481. 10.1016/j.jalz.2018.01.010 [PubMed: 29499171]

Iadecola C, 2004. Neurovascular regulation in the normal brain and in Alzheimer's disease. Nat. Rev. Neurosci 5, 347–360. 10.1038/nrn1387 [PubMed: 15100718]

Johnson LA, Cushing B, Rohlfing G, Edwards M, Davenloo H, D'Agostino D, Hall JR, O'Bryant SE, 2014. The Hachinski Ischemic Scale and cognition: The influence of ethnicity. Age Ageing 43, 364–369. 10.1093/ageing/aft189 [PubMed: 24321843]

Lane CA, Barnes J, Nicholas JM, Sudre CH, Cash DM, Parker TD, Malone IB, Lu K, James SN, Keshavan A, Murray-Smith H, Wong A, Buchanan SM, Keuss SE, Gordon E, Coath W, Barnes A, Dickson J, Modat M, Thomas D, Crutch SJ, Hardy R, Richards M, Fox NC, Schott JM, 2019. 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 18, 942–952. 10.1016/S1474-4422(19)30228-5 [PubMed: 31444142]

Lattanzi S, Vernieri F, Silvestrini M, 2018. Blood pressure variability and neurocognitive functioning. J. Clin. Hypertens 20, 645–647. 10.1111/jch.13232

Ma Y, Wolters FJ, Chibnik LB, Licher S, Ikram MA, Hofman A, Ikram MK, 2019. Variation in blood pressure and long-term risk of dementia: a population-based cohort study. PLoS Med 16, 1–16. 10.1371/journal.pmed.1002933

Mattsson N, Tosun D, Insel PS, Simonson A, Jack CR, Beckett LA, Donohue M, Jagust W, Schuff N, Weiner MW, 2014. Association of brain amyloid-β with cerebral perfusion and structure in Alzheimer's disease and mild cognitive impairment. Brain 137, 1550–1561. 10.1093/brain/awu043 [PubMed: 24625697]

Nagai M, Dote K, Kato M, Sasaki S, Oda N, Kagawa E, Nakano Y, Yamane A, Higashihara T, Miyauchi S, Tsuchiya A, 2017. Visit-to-visit blood pressure variability and Alzheimer's disease: Links and risks. J. Alzheimer's Dis 59, 515–526. 10.3233/JAD-161172 [PubMed: 28598842]

Nagai M, Hoshide S, Kario K, 2010. The insular cortex and cardiovascular system: a new insight into the brain-heart axis. J. Am. Soc. Hypertens 4, 174–182. [PubMed: 20655502]

Oishi E, Ohara T, Sakata S, Fukuhara M, Hata J, Yoshida D, Shibata M, Ohtsubo T, Kitazono T, Kiyohara Y, Ninomiya T, 2017. Day-to-day blood pressure variability and risk of dementia in

a general Japanese elderly population: The Hisayama study. Circulation 136, 516–525. 10.1161/CIRCULATIONAHA.116.025667 [PubMed: 28784822]

Petersen RC, Aisen PS, Beckett LA, Donohue MC, Gamst AC, Harvey DJ, Jack CR, Jagust WJ, Shaw LM, Toga AW, Trojanowski JQ, Weiner MW, 2010. Alzheimer's Disease Neuroimaging Initiative (ADNI): Clinical characterization. Neurology 74, 201–209. 10.1212/WNL.0b013e3181cb3e25 [PubMed: 20042704]

Qin B, Viera AJ, Muntner P, Plassman BL, Edwards LJ, Adair LS, Popkin BM, Mendez MA, 2016. Visit-to-visit variability in blood pressure is related to late-life cognitive decline. Hypertension 68, 106–113. 10.1161/HYPERTENSIONAHA.116.07494 [PubMed: 27217401]

Qiu C, Winblad B, Fratiglioni L, 2005. The age-dependent relation of blood pressure to cognitive function and dementia. Lancet Neurol 4, 487–499. 10.1016/S1474-4422(05)70141-1 [PubMed: 16033691]

R Core Team, 2018. R: A language and environment for statistical computing

Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, Sever PS, Poulter NR, 2010. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet 375, 895–905. 10.1016/S0140-6736(10)60308-X [PubMed: 20226988]

Rouch L, Cestac P, Sallerin B, Piccoli M, Benattar-Zibi L, Bertin P, Berrut G, Corruble E, Derumeaux G, Falissard B, Forette F, Pasquier F, Pinget M, Ourabah R, Danchin N, Hanon O, Vidal JS, 2020. Visit-to-visit blood pressure variability is associated with cognitive decline and incident dementia: The S.AGES cohort. Hypertension 76, 1280–1288. 10.1161/HYPERTENSIONAHA.119.14553 [PubMed: 32862710]

Seibyl J, Shaw LM, Blennow K, Widmann M, Corradini V, Wahl S, Zink K, Buck K, Eichenlaub U, Hansson O, 2017. Amyloid-PET concordance of Elecsys® CSF biomarker immunoassays for Alzheimer's disease. Alzheimer's Dement 13, P199–P200. 10.1016/j.jalz.2017.07.062

Shaw LM, Fields L, Korecka M, Waligórska T, Trojanowski JQ, Allegranza D, Bittner T, He Y, Morgan K, Rabe C, 2016. 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 12, P668. 10.1016/j.jalz.2016.06.1513

Shaw LM, Waligorska T, Fields L, Korecka M, Figurski M, Trojanowski JQ, Eichenlaub U, Wahl S, Quan M, Pontecorvo MJ, Lachno DR, Talbot JA, Andersen SW, Siemers ER, Dean RA, 2018. Derivation of cutoffs for the Elecsys® amyloid β (1–42) assay in Alzheimer's disease. Alzheimer's Dement. Diagnosis, Assess. Dis. Monit 10, 698–705. 10.1016/j.dadm.2018.07.002

Sible IJ, Nation DA, Alzheimer's Disease Neuroimaging Initiative, 2020. Long-term blood pressure variability across the clinical and biomarker spectrum of Alzheimer's disease. J. Alzheimer's Dis 77, 1655–1669. 10.3233/JAD-200221 [PubMed: 32925032]

Webb AJ, Fischer U, Mehta Z, Rothwell PM, 2010. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: A systematic review and meta-analysis. Lancet 375, 906–915. 10.1016/S0140-6736(10)60235-8 [PubMed: 20226989]

Wolters FJ, Zonneveld HI, Hofman A, Van Der Lugt A, Koudstaal PJ, Vernooij MW, Ikram MA, 2017. Cerebral perfusion and the risk of dementia: A population-based study. Circulation 136, 719–728. 10.1161/CIRCULATIONAHA.117.027448 [PubMed: 28588075]

Yew B, Nation DA, 2017. Cerebrovascular resistance: Effects on cognitive decline, cortical atrophy, and progression to dementia. Brain 140, 1987–2001. 10.1093/brain/awx112 [PubMed: 28575149]

Yoo JE, Shin DW, Han K, Kim D, Lee SP, Jeong SM, Lee J, Kim SY, 2020. Blood pressure variability and the risk of dementia: a nationwide cohort study. Hypertension 75, 982–990. 10.1161/HYPERTENSIONAHA.119.14033 [PubMed: 32148122]

Zlokovic BV, 2011. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. Nat. Rev. Neurosci 12, 723–738. 10.1038/nrn3114 [PubMed: 22048062]

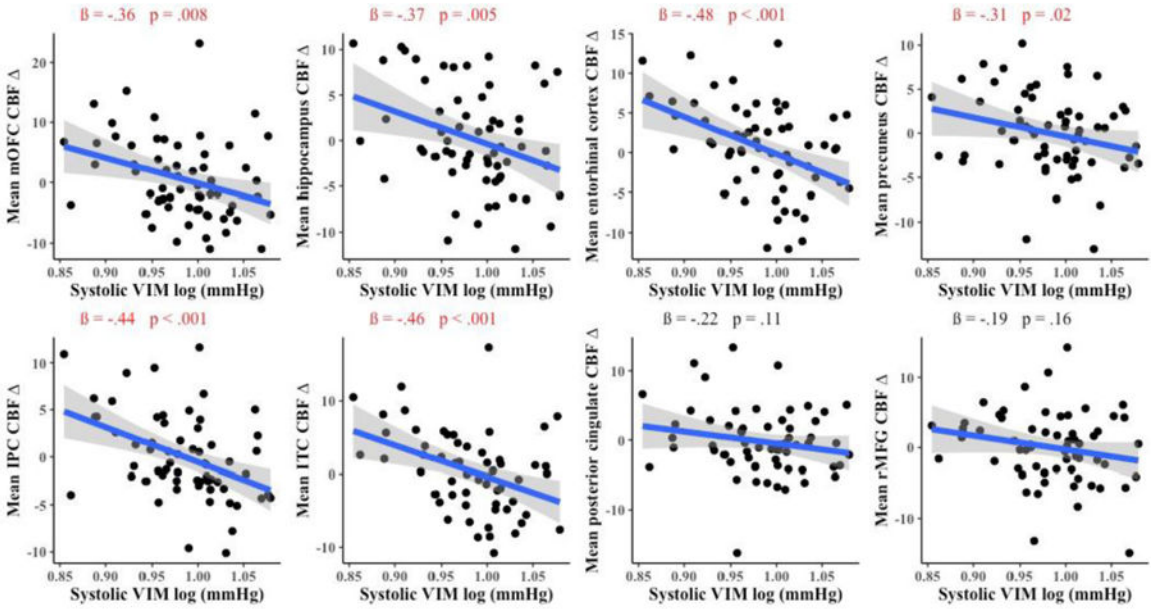

Figure 1. Elevated systolic BPV is related to regional CBF decline in older adults without dementia

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

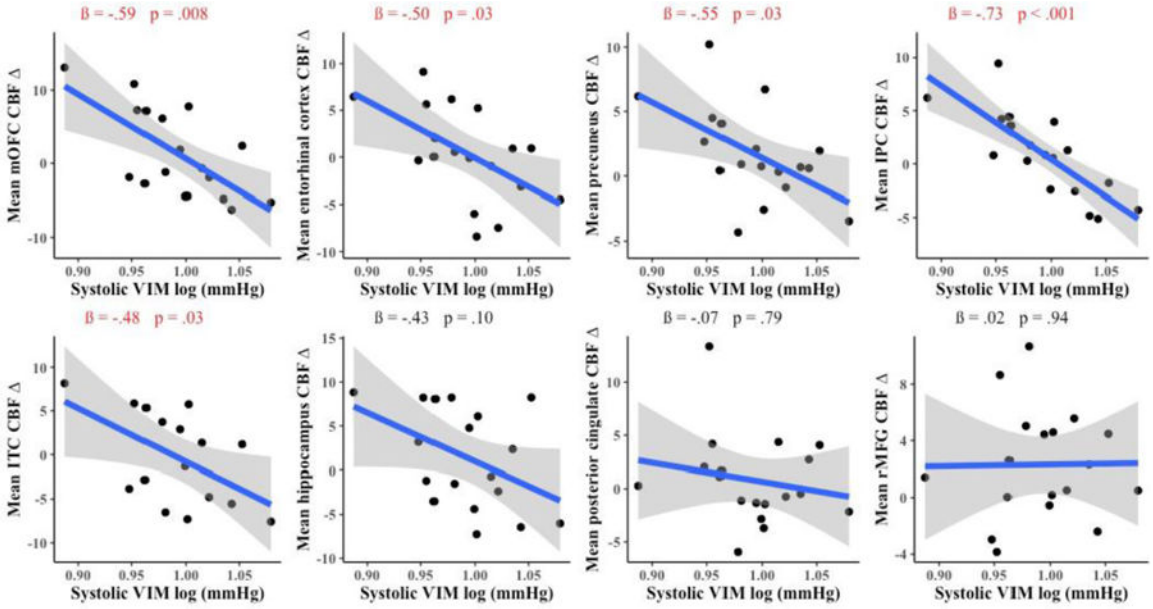

Figure 2. Elevated systolic BPV is linked to regional CBF decline in older adults with Aβ abnormality

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

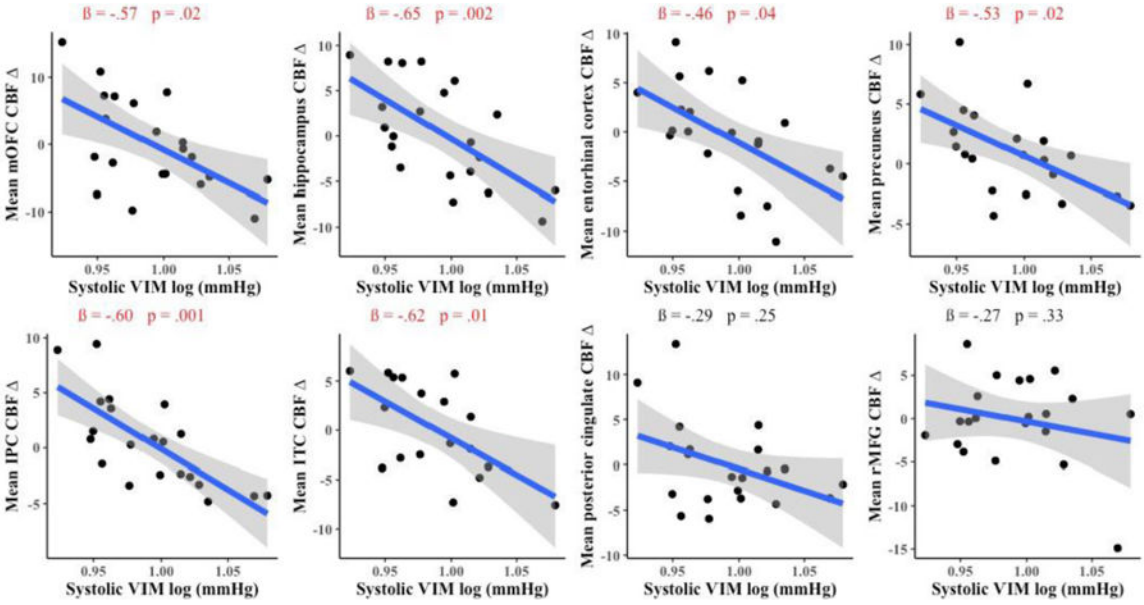

Figure 3. Elevated systolic BPV is linked to regional CBF decline in older adults with Ptau abnormality

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

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