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Selective vulnerability of medial temporal regions to short-term blood pressure variability and cerebral hypoperfusion in older adults

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Abstract

Blood pressure variability is an emerging risk factor for stroke, cognitive impairment, and dementia, possibly through links with cerebral hypoperfusion. Recent evidence suggests visit-to-visit (e.g., over months, years) blood pressure variability is related to cerebral perfusion decline

[1]Abbreviations: BP = blood pressure; BPV = blood pressure variability; AD = Alzheimer's disease; CBF = cerebral blood flow; pCASL-MRI = pseudo-continuous arterial spin-labelling MRI; ROI = regions-of-interest; mOFC = medial orbitofrontal cortex; IPC = inferior parietal cortex; ITC = inferior temporal cortex; rMFG = rostral middle frontal gyrus; VIM = variation independent of mean; CV = coefficient of variation; BMI = body mass index; DRS-2 = Mattis Dementia Rating Scale – 2; FDR = false discovery rate; FWE = family-wise error; APOE ϵ4 = apolipoprotein ϵ4

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in brain regions vulnerable to Alzheimer's disease. However, less is known about relationships between short-term (e.g., < 24 hours) blood pressure variability and regional cerebral perfusion, and whether these relationships may differ by age. We investigated short-term blood pressure variability and concurrent regional cerebral microvascular perfusion in a sample of community-dwelling older adults without history of dementia or stroke and healthy younger adults. Blood pressure was collected continuously during perfusion MRI. Cerebral blood flow was determined for several brain regions implicated in cerebrovascular dysfunction in Alzheimer's disease. Elevated systolic blood pressure variability was related to lower levels of concurrent cerebral perfusion in medial temporal regions: hippocampus (β = −.60 [95% CI −.90, −.30]; $p < .001$), parahippocampal gyrus (β = −.57 [95% CI −.89, −.25]; $p = .001$), entorhinal cortex (β = −.42 [95% CI −.73, −.12]; $p = .009$), and perirhinal cortex (β = −.37 [95% CI −.72, −.03]; $p = .04$), and not in other regions, and in older adults only. Findings suggest a possible age-related selective vulnerability of the medial temporal lobes to hypoperfusion in the context of short-term blood pressure fluctuations, independent of average blood pressure, white matter hyperintensities, and gray matter volume, which may underpin the increased risk for dementia associated with elevated BPV.[1]

Keywords

blood pressure variability; cerebral hypoperfusion; aging; medial temporal lobes

1. INTRODUCTION

Blood pressure (BP) and cerebral perfusion are related to dementia risk (Lane et al., 2019; Mattsson et al., 2014; Wolters et al., 2017; Yew and Nation, 2017; Zlokovic, 2011). Growing evidence suggests that increased BP variability (BPV) over the long-term (e.g., months, years, also known as "visit-to-visit BPV") and short-term (e.g., < 24 hours) are also associated with increased risk for, and predictive of, cognitive impairment and dementia, including Alzheimer's disease (AD) and vascular dementia, regardless of average BP levels (De Heus et al., 2021; Lattanzi et al., 2018, 2014; Ma et al., 2020b; Nagai et al., 2017; Oishi et al., 2017; Qin et al., 2016; Tully et al., 2020). A recent study found that BPV elevation may occur before the onset of major neurocognitive dysfunction and in the context of ongoing AD pathophysiology, suggesting a potentially useful early marker of disease progression that is both readily accessible and easily modifiable (Sible et al., 2020). It is widely appreciated that vascular factors contribute to 30–75% of cases of AD (Schneider et al., 2007) and a growing number of studies now focus on how BPV may be one such vascular factor linked to increased dementia risk.

Although possible mechanisms linking BPV to increased dementia risk are not well known, it has been proposed that elevated BPV may jeopardize cerebral perfusion and disrupt neuronal functioning (Lattanzi et al., 2018; Ma et al., 2020b). Chronic large fluctuations in BP may stress arterial walls beyond repair and promote arterial remodeling and microvascular damage (Ma et al., 2020c, 2020a). Indeed, elevated BPV has been linked with stroke (Kato et al., 2010; Parati et al., 2018), arterial stiffness (Schillaci et al., 2012; Tatasciore et al., 2020; Xia et al., 2017), and cerebrovascular disease burden on MRI (e.g.,

white matter hyperintensities, cortical infarcts, cerebral microbleeds) (Ma et al., 2020a) and at postmortem evaluation (e.g., atherosclerosis in the Circle of Willis, arteriolosclerosis) (Sible et al., 2021a), independent of average BP. These microvascular changes may alter blood-brain barrier integrity and risk hypoperfusion injury (Lattanzi et al., 2018). Consistent with this hypothesis, a recent study found that elevated BPV was related to cerebral perfusion decline in brain regions associated with cerebrovascular dysfunction in AD (Sible et al., 2021b). Importantly, this repeated "tsunamic effect" in the cerebral parenchyma may be particularly relevant in aging, due to the possibility that age-related arterial stiffening may further amplify BPV (Ma et al., 2020b; Nagai et al., 2017; Schillaci et al., 2012; Tatasciore et al., 2020; Xia et al., 2017; Yoo et al., 2020), and in brain areas both highly sensitive to BP-related hypoxic-ischemic injury and vulnerable to early blood-brain barrier breakdown and AD, such as the medial temporal lobes (Iadecola, 2004; Ma et al., 2020b; Nation et al., 2019; Schmidt-Kastner and Freund, 1991; Vikner et al., 2021).

While the dynamic relationship governing BP changes and cerebral blood flow (CBF) have been well-studied using transcranial doppler (Aaslid et al., 1989), the majority of this literature is limited to studying blood flow velocity in the larger intracranial arteries (D'Andrea et al., 2016). Less is known about the role of BPV in regional cerebral microvascular perfusion, where smaller vascular compartments are critical to blood-brain barrier nutrient transfer, nutrient influx, and waste clearance essential for neuronal functioning (Kisler et al., 2017; Zlokovic, 2011). It is also unclear whether relationships may differ by age. To investigate these possibilities, we studied short-term BPV during concurrent assessment of regional cerebral microvascular perfusion in a sample of older and younger adults.

2. MATERIAL AND METHODS

2.1 Participants

Study participants were drawn from the Vascular Senescence and Cognition Lab at the University of Southern California (USC), an ongoing research study aimed at detailing various vascular mechanisms of cognitive decline and dementia. Participants were recruited from the community via flyers and related research list-serves at USC. Inclusion criteria included aged 55–90 and living independently in the greater Los Angeles area. Participants were excluded for history of dementia, stroke, traumatic brain injury, learning disability, or other systemic or neurological disorder known to affect the central nervous system. Additionally, all research participants underwent neuropsychological testing that included the Mattis Dementia Rating Scale – 2 (DRS-2) (Griffiths et al., 2011), a widely used measure of global cognition. Remaining eligible participants were further excluded based on a DRS-2 total score ≤ 126, an established cutoff to rule out major neurocognitive impairment (Griffiths et al., 2011). A sample of healthy younger adults were also recruited from the USC campus. The study was approved by the Institutional Review Board at USC and all participants provided their written informed consent.

The present study included 33 older adult participants (ages 55–87) and 26 younger adult participants (ages 18–28) who underwent resting pseudo-continuous arterial spin-labelling MRI (pCASL-MRI) with simultaneous, continuous BP monitoring.

2.2 Measures

2.2.1 Cerebral perfusion assessment—CBF was determined from a 5-minute resting pCASL-MRI on a single 3 Tesla Siemens® MAGNETOM Prisma MRI using a pCASL method with background suppressed gradient and spin echo (GRASE) readout. The following parameters were used: TR = 5000ms; TE = 36.3ms; FOV = 240mm; resolution = 2.5×2.5×3.4mm^3; slice thickness = 3.42mm; number of slices = 24; number of measurements = 1 M0 image + 1 dummy image + 15 pairs of tag-control images; total scan time = 5:25. pCASL scans were co-registered to structural T1 MRI scans collected during the same session. CBF was determined for several *a priori* regions-of-interest (ROI) linked to hypoperfusion-related dementia risk (Mattsson et al., 2014; Yew and Nation, 2017): hippocampus, entorhinal cortex, posterior cingulate, precuneus, medial orbitofrontal cortex (mOFC), inferior parietal cortex (IPC), inferior temporal cortex (ITC), and rostral middle frontal gyrus (rMFG). We also included ROIs for other medial temporal regions (e.g., parahippocampal gyrus and perirhinal cortex), given the known associations with both BP-related hypoxic-ischemic injury vulnerability and AD pathology in this region (Iadecola, 2004; Schmidt-Kastner and Freund, 1991; Vikner et al., 2021; Zlokovic, 2011). ROIs were derived from the AAL3 atlas (Rolls et al., 2020) and warped into MNI standard space. CBF values were normalized to precentral gyrus CBF during the MRI, due to the relative sparing of this region in AD, and consistent with other studies of perfusion MRI in older adults, as described elsewhere (Mattsson et al., 2014; Sible et al., 2021b; Yew and Nation, 2017). Finally, values were averaged across hemispheres and used in all analyses. Whole brain CBF was also determined.

2.2.2 BP assessment—BP was collected continuously using a Biopac® MRI-compatible BP monitoring device during the 5-minute resting pCASL-MRI scan. BP data were then processed offline using a custom pipeline scripted in AcqKnowledge®, as described elsewhere (Sturm et al., 2018b). Briefly, BP signals were first visually inspected for mechanical errors and noise (e.g., signal dropout due to sensor interference) and then algorithms detected and removed any outliers defined as +/− 3 standard deviations (SD) from the average over the entire resting 5-minute scan. Intraindividual BPV was calculated as variation independent of mean (VIM), a commonly used measure of BPV uncorrelated with mean BP levels (de Heus et al., 2019; Peter M. Rothwell et al., 2010; Rouch et al., 2020; Sible et al., 2021b, 2020; Xia et al., 2017). VIM was calculated as: VIM = SD/mean^x, where the power x was derived from non-linear curve fitting of BP SD against average BP using the nls package in R Project, as previously described (Peter M. Rothwell et al., 2010; Sible et al., 2021b, 2021a, 2020). To use measures of BPV that may be more readily computed in clinical settings, intraindividual BPV was also calculated as the SD and coefficient of variation (CV [100 × SD/mean]) (see Supplementary Materials). Evidence suggests all three indices capture relationships between BPV and cardiovascular and cognitive outcomes (de Heus et al., 2019; Parati et al., 2018, 2013; Peter M. Rothwell et al., 2010; Yano, 2017), but unlike SD, CV and VIM offer information uncorrelated with mean levels. Furthermore, VIM was recently shown to better predict all-cause mortality in the SPRINT dataset when compared to other indices of BPV (Cheng et al., 2021).

2.2.3 Brain gray matter volume assessment—

Participants underwent structural brain MRI to obtain T1-weighted magnetization prepared rapid gradient-echo (MP-RAGE) sequence for high resolution anatomical images using the following scan parameters: TR = 2300 ms; TE = 2.98 ms; TI = 900 ms; slice thickness = 1.20 mm; flip angle = 9°; field of view = 256 mm. Structural T1 scans were processed using Freesurfer (Dale et al., 1999; Ségonne et al., 2004) and gray matter volumes were extracted for the same ROIs in CBF analyses described above.

2.2.4 White matter hyperintensity assessment—

A subset of older adult participants (n = 32 out of 33) also underwent T2-fluid attenuated inversion recovery (FLAIR) MRI sequence for the evaluation of white matter lesions. The following parameters were used: TR = 10000 ms; TE = 91 ms; TI = 2500 ms; slice thickness = 5.0 mm; flip angle = 150°; field of view = 220 mm. Severity of white matter hyperintensities was determined by visual grading with a recognized scale (Fazekas et al., 1987): 0 = “absent”; 1 = “caps or pencil-thin lining around ventricles or discrete diffuse lesions”; 2 = “smooth halo around ventricles or beginning of confluence of foci”; 3 = “irregular PVH extending into the DWM or large confluent areas”.

2.2.5 Other measurements—

Demographic, clinical, and cognitive information was determined from study screening. Height and weight were collected to determine body mass index (BMI) (weight (kg) / height (meters) squared). Medication use was also assessed, and participants were categorized as those taking antihypertensive medication (all classes) versus those not taking antihypertensive medication. Older adult participants also underwent neuropsychological testing that included the DRS-2 (Griffiths et al., 2011), a widely used measure of global cognition. Total raw scores (max score = 144) were then converted to age-corrected scaled scores (Lucas et al., 1998).

2.3 Statistical Analysis

BPV values were log-transformed to approach a normal distribution. ANOVA and chi-square tests compared older and younger adults on clinical and demographic variables as well as CBF levels. Multiple linear regression was first used to investigate the relationship between BPV and regional CBF in older and younger adults separately. To limit the risk of type 1 error and leverage knowledge gained from prior ASL-MRI studies in older adults (Mattsson et al., 2014; Yew and Nation, 2017), voxel-wise multivariable regressions were then performed with explicit masks of ROIs found to be significant in initial analyses. All models controlled for age, sex, and antihypertensive medication use. Supplementary analyses explored associations using the SD and CV indices of BPV, as well as relationships between 1) BPV and whole brain CBF, and 2) average BP and regional CBF. Elevated BPV is thought to be influenced by sympathetic nervous system overactivity (Imai et al., 1997; Mancia et al., 1997; Parati et al., 2018, 2013), which has been shown to be lateralized to the brain’s right hemisphere in studies of older adults (Guo et al., 2016; Sturm et al., 2018a). Therefore, exploratory analyses examined relationships between BPV and CBF by hemisphere in ROIs found to be significant in initial analyses. Potential lateralization effects were formally tested by adding an interaction term of hemisphere to regression models. Based on a power analysis for detecting moderate-to-large effect sizes using G*Power (Faul

et al., 2009), multiple linear regression ($\alpha = .05$, 3 covariates) with a sample size of 28 older adults will yield 85% power. As such, the current study is adequately powered to detect moderate-to-large effect sizes in analyses of older adults, while analyses of younger adults should be regarded as exploratory. Sensitivity analyses tested the robustness of primary findings by substituting antihypertensive use, to preserve statistical power, for 1) severity of white matter hyperintensities (e.g., Fazekas score), 2) brain gray matter volume in the corresponding ROI, 3) BMI, 4) years of education, and 5) global cognition (e.g., DRS-2 total scaled score). All analyses were 2-sided with significance set at $p < .05$ for ROI regression and family-wise error (FWE) corrected $p < .05$ for voxel-wise regression. False Discovery Rate (FDR) (Benjamini and Hochberg, 1995) was set at $p < .05$ for ROI analyses. All analyses were carried out in R Project (R Core Team, 2018).

3. RESULTS

As shown in Table 1, older adults were significantly older, had greater BMI, and had greater systolic BP when compared to younger adults. Additionally, CBF was significantly lower in older adults when compared to younger adults in the following ROIs: hippocampus, posterior cingulate, precuneus, mOFC, IPC, ITC, and rMFG.

3.1 ROI analyses

ROI analyses revealed elevated systolic BPV in older adults was related to lower CBF in medial temporal lobe regions: hippocampus ($\beta = -.60$ [95% CI −.90, −.30]; $p < .001$; $R^2 = .43$), parahippocampal gyrus ($\beta = -.57$ [95% CI −.89, −.25]; $p = .001$; $R^2 = .35$), entorhinal cortex ($\beta = -.42$ [95% CI −.73, −.12]; $p = .009$; $R^2 = .42$), and perirhinal cortex ($\beta = -.37$ [95% CI −.72, −.03]; $p = .04$; $R^2 = .25$), but findings did not reach statistical significance in other regions (p's = .08 to .99) (Figure 1). Diastolic BPV in older adults was not related to CBF in any region (p's = .16 to .99) (Data not shown). BPV in younger adults was not related to regional CBF (systolic: p's = .18 to .95; diastolic: p's = .12 to .90) (Data not shown).

After FDR correction, systolic BPV findings in older adults remained significant for all regions except for perirhinal cortex (q-value = .10).

3.2 Voxel-wise analyses

Voxel-wise analyses restricted to medial temporal lobe showed elevated systolic BPV in older adults was related to lower cerebral perfusion in the bilateral medial temporal lobe with the right-sided clusters significant after FWE correction (20, −32, −12; peak $T = 3.93$) (Figure 2).

3.3 Supplementary analyses

Supplementary analyses using the SD and CV indices of BPV revealed similar relationships with regional CBF in older adults (see Supplementary Results).

No significant relationships were observed between BPV and whole brain CBF (p's = .48 to .70), or between average BP and CBF in any ROI in either older adults or younger adults (p's = .11 to .97) (see Supplementary Results).

3.4 Exploratory analyses

Primary results did not differ significantly by hemisphere (p's = .63 to .91) (Data not shown).

3.5 Sensitivity analyses

Primary findings were essentially unchanged when controlling for severity of white matter hyperintensities, brain gray matter volume in the corresponding ROI, BMI, years of education, and global cognition (see Supplementary Results).

4. DISCUSSION

Findings indicate that elevated short-term systolic BPV was related to lower concurrent CBF in medial temporal regions known to convey hypoperfusion-related dementia risk in older adults, independent of average BP levels. In contrast, no relationships between BPV and CBF were observed in younger adults or in regions beyond the medial temporal lobe, suggesting an age-dependent relationship between short-term BPV and CBF specifically within medial temporal regions.

The present study used a novel approach of monitoring BP during assessment of regional microvascular perfusion and was thus able to appreciate any relationships between short-term BPV and concurrent regional CBF. While a recent study found that visit-to-visit BPV is linked with cerebral perfusion decline in several brain regions associated with cerebrovascular dysfunction in AD, including medial temporal lobes (Sible et al., 2021b), the present investigation suggests the medial temporal lobes may also be particularly susceptible to short-term BP fluctuations. Prior studies suggest selective regional vulnerability of medial temporal structures to hypoperfusion during hypotensive crisis (Schmidt-Kastner and Freund, 1991). Animal models have also shown that CA1 neurons and capillaries in the hippocampus are sensitive to impaired microcirculation (De Jong et al., 1999). Additionally, a recent study found that hippocampal vascularization patterns were related to memory performance and hippocampal volume, especially in individuals with cerebrovascular disease (Perosa et al., 2020). Furthermore, hypoperfusion in the medial temporal lobes has been linked with cognitive impairment, including worse performance on tests of memory, and increased risk for AD (Bangen et al., 2021; Wierenga et al., 2014). Although causality cannot be determined based on cross-sectional observations, the present study findings could suggest a selective vulnerability of medial temporal structures to hypoperfusion in the context of short-term BP fluctuation. It is, therefore, possible that the increased risk for dementia associated with elevated short-term BPV may be related to hypoperfusion of medial temporal regions critical for memory function.

Arterial stiffening may influence the relationship between BPV and CBF. Specifically, arterial stiffening may alter pulse wave dynamics and amplify BPV, further exacerbating the impact of BP changes on brain health and cognition (Lattanzi et al., 2018; Ma et al., 2020b;

Nagai et al., 2017; Tatasciore et al., 2020; Yoo et al., 2020; Zhou et al., 2018). Older adults may be particularly vulnerable to these vascular changes, given the significant role age is known to play in the development of arterial stiffening (Zhou et al., 2018). Consistent with this hypothesis, several studies report links between elevated BPV in older adults, arterial stiffness, and cognitive impairment (Schillaci et al., 2012; Winder et al., 2021; Xia et al., 2017). Additionally, arterial stiffening may contribute to the growing evidence linking BPV to cerebrovascular disease by disrupting tissue perfusion to the brain's microvasculature (Ma et al., 2020a). Arterial stiffness is strongly associated with atherosclerosis (Van Popele et al., 2001), a well-studied risk factor for AD, possibly through links with altered CBF and subsequent microinfarction (Arvanitakis et al., 2016; Hofman et al., 1997; Toledo et al., 2013; White et al., 2002). Recent evidence suggests elevated BPV is related to increased severity of atherosclerosis in the Circle of Willis and arteriolosclerosis in the brain's smaller arteries relevant to microvascular perfusion (Ma et al., 2021; Sible et al., 2021a). Importantly, the Circle of Willis includes the posterior cerebral artery and anterior choroidal artery, which both perfuse the highly vulnerable hippocampi (Perosa et al., 2020). While the current study did not directly investigate links with arterial stiffness, more studies are needed to determine whether this may be related to the increased risk for AD associated with elevated BPV.

Other age-related vascular changes, such as diminished baroreflex sensitivity, may also be responsible for the observed relationship between short-term BPV and medial temporal hypoperfusion in older adults only (Lattanzi et al., 2018; Nagai et al., 2017). Several autoregulatory mechanisms, including baroreflex sensitivity, work to steady naturally dynamic BP levels in order to maintain steady perfusion levels needed to meet the brain's high metabolic demand (Parati et al., 2013; Zlokovic, 2011). However, age-related declines in baroreflex sensitivity may leave BP less regulated and risk frequent, but mild reductions in CBF (Coats et al., 1991; Conway et al., 1985; Imai et al., 1997). These reductions, known as oligemia, have been associated with severe cell disruption and cognitive impairment (Zlokovic, 2011). Future work will examine links with baroreflex sensitivity.

BPV is linked with antemortem and postmortem markers of cerebrovascular disease (Ma et al., 2020a; Sible et al., 2021a). Study findings suggest short-term BPV is related to lower levels of medial temporal lobe CBF, even in a sample of older adults with limited cerebrovascular disease. Results remained even after sensitivity analyses controlled for severity of white matter hyperintensities; however, the sample notably had minimal white matter hyperintensity burden (e.g., 72% had Fazekas scores ≤ 1). More studies should investigate relationships in samples with varying levels of cerebrovascular disease burden.

Neurodegeneration effects on cortical control of the autonomic nervous system could alternatively help explain the study findings. Specifically, atrophy of these regions may disrupt autonomic function and leave both BP and CBF less regulated (Kitamura et al., 2020). However, consistent with a recent study of visit-to-visit BPV and cerebral perfusion decline (Sible et al., 2021b), findings were independent of gray matter volume, lending further support to the hypothesis that BPV may be related to CBF through a vascular mechanism.

AD risk gene apolipoprotein ϵ4 (APOE ϵ4) has been associated with neuronal and neurovascular dysfunction in the medial temporal lobes (Burggren et al., 2008; Palop and Mucke, 2011). It was recently reported that APOE ϵ4 carriers display early blood-brain barrier breakdown in the medial temporal lobes (Montagne et al., 2020), and that this was predictive of cognitive impairment (Nation et al., 2019), independent of AD pathology. Larger studies adequately powered to examine relationships between BPV and CBF based on APOE ϵ4 carrier status will help elucidate vascular contributions of APOE ϵ4 to AD risk.

A study strength is the continuous collection of BP during perfusion MRI, which allowed exploration of concurrent relationships between short-term BPV and CBF. Additionally, the study used pCASL-MRI to quantify microvascular perfusion, which captures flow in the smallest vascular compartments critical to nutrient transfer and blood-brain barrier integrity, in brain areas with known importance for cognition and AD. The study adds to our understanding of potential age-related relationships between short-term BP changes and cerebral perfusion by utilizing a sample of both older and younger adults. Findings were present in a sample of community-dwelling older adults without history of dementia or stroke, even after controlling for global cognition, bolstering prior evidence suggesting BPV elevation precedes major neurocognitive dysfunction (Sible et al., 2020), with potential therapeutic implications. Study findings add to the growing clinical relevance of BPV as a risk factor for and predictor of cognitive decline (De Heus et al., 2021; Lattanzi et al., 2014) and cerebrovascular disease severity (Tully et al., 2020), above and beyond average BP levels.

The current study is limited by the small sample size. Relatedly, while findings controlled for antihypertensive medication use, the study was not adequately powered to detect potential class effects of antihypertensive treatment on BPV and CBF. Some evidence suggests differential class effects on BPV in risk for stroke, independent of average BP levels (Peter M Rothwell et al., 2010; Webb et al., 2010). Future studies with large sample sizes that investigate possible class effects of monotherapy and combination therapy may have the potential to inform antihypertensive treatment decisions. Other indices of short-term BPV, such as 24-hour monitoring, provide information on BP changes relevant to the circadian rhythm, such as nighttime “dipping” (Parati et al., 2013). Relatedly, scans were collected at variable times throughout the day (e.g., between the hours of 8 AM and 5 PM), which may obscure the influence of typical daytime/nighttime BP changes (Parati et al., 2013). While the methods used in the current investigation do not capture this phenomenon, beat-to-beat BPV offers assessment of cardiovascular modulation that 24-hour BPV does not. Nevertheless, both indices of BPV have been linked with cardiovascular and cognitive outcomes (Cho et al., 2018; Oishi et al., 2017; Parati et al., 2013; Schillaci et al., 2012; Tatasciore et al., 2020; Xia et al., 2017; Zhou et al., 2018) and the reliability of these different time windows remains unclear (Parati et al., 2013). Additionally, the cross-sectional design limits interpretation of findings. Another study limitation is the lack of characterization of AD biomarkers amyloid-beta and phosphorylated tau. While findings were largely unchanged when controlling for one marker of neurodegeneration (e.g., gray matter volume), including AD biomarkers will help elucidate potential relationships in the context of ongoing AD biomarker abnormality.

5. CONCLUSIONS

Elevated short-term BPV is related to lower, concurrent levels of CBF specifically in the medial temporal lobes, independent of average BP, in older adults only. Medial temporal lobes may have an age-related selective vulnerability to hypoperfusion in the context of short-term BP fluctuation, which may underpin the increased risk for dementia associated with elevated BPV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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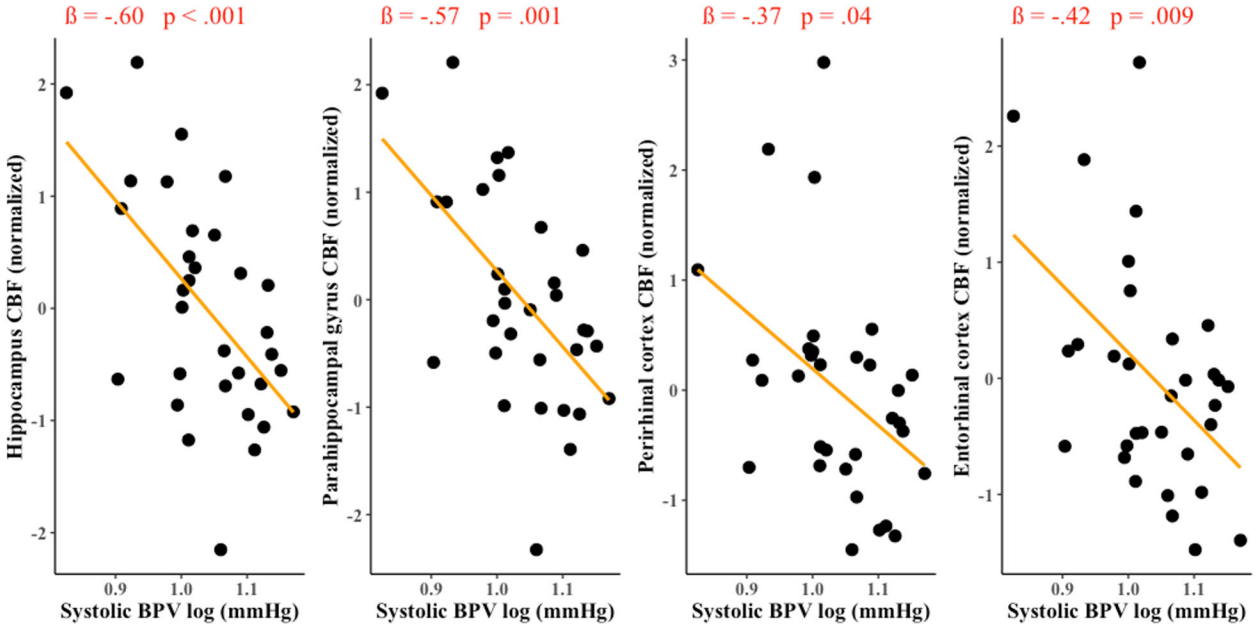

Figure 1. Elevated short-term systolic BPV is related to lower concurrent medial temporal cerebral perfusion in older adults

Scatterplots display the relationship between short-term systolic BPV and corrected microvascular perfusion in medial temporal regions in older adults. CBF values were adjusted for age, sex, and antihypertensive medication use.

Abbreviations: BPV = blood pressure variability

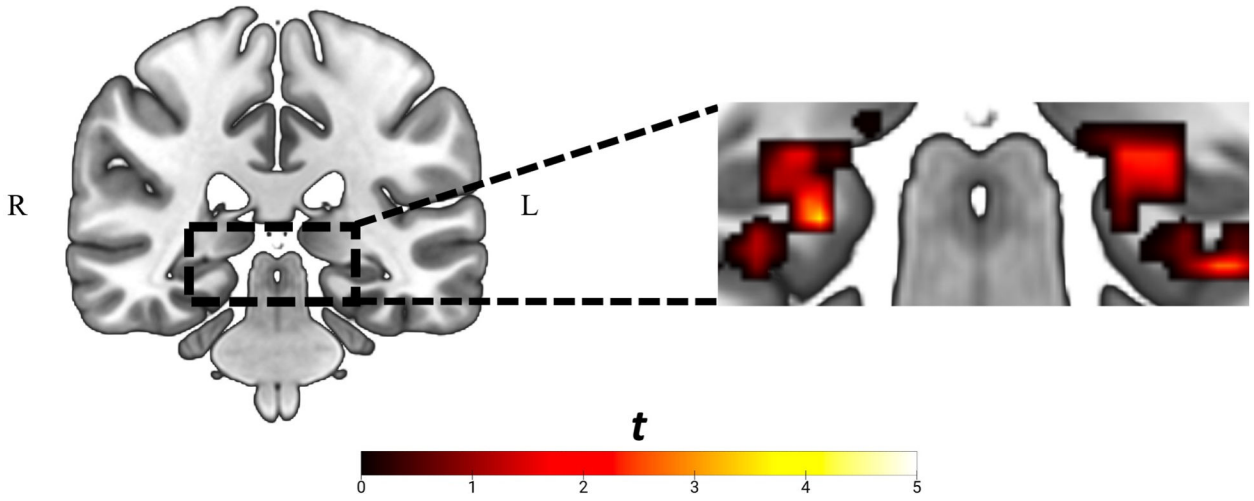

Figure 2. Voxel-wise associations between short-term BPV and medial temporal perfusion in older adults

Results of voxel-wise analyses in the medial temporal lobes in older adults.

Table 1.

Demographic and clinical information for older and younger adults.

	Older Adult (*n*=33)	**Younger Adult (*n*=26)**	***F* or χ^2**	***p*-value**
Age (years)	68.7 (8.5)	22.0 (2.7)	725.3	**<.001**
Sex (male/female)	14/19	6/20	1.64	.20
Education (years)	16.3 (2.8)	--	--	--
APOE-ϵ4 carriers (*n*, %)	12 (36.4%)	--	--	--
DRS-2 total (scaled score)	11.6 (2.5)	--	--	--
Body mass index (kg/m^2)	26.5 (5.5)	23.0 (3.5)	7.90	**.007**
Fazekas score (*n*, %)				
0	4 (12.5%)	--	--	--
1	19 (59.4%)	--	--	--
2	7 (21.9%)	--	--	--
3	2 (6.3%)	--	--	--
Antihypertensive use (*n*, %)	13 (39.4%)	--	--	--
Systolic BP (mmHg)	132.5 (22.0)	110.0 (21.8)	15.26	**<.001**
Diastolic BP (mmHg)	79.2 (20.4)	78.7 (25.7)	.01	.94
Systolic BPV (mmHg)	10.1 (2.0)	9.4 (1.8)	2.00	.16
Diastolic BPV (mmHg)	5.7 (1.0)	6.3 (1.1)	3.96	.05
CBF (ml/100g/min)				
Hippocampus	39.2 (6.5)	44.3 (5.9)	4.99	**.03**
Parahippocampal gyrus	44.5 (6.4)	44.5 (6.0)	2.59	.11
Entorhinal cortex	50.4 (7.5)	48.9 (5.2)	.78	.38
Perirhinal cortex	43.0 (6.5)	45.6 (6.7)	.002	.97
Posterior cingulate	51.8 (10.7)	65.4 (12.6)	20.14	**<.001**
Precuneus	46.8 (7.5)	57.1 (9.7)	21.03	**<.001**
mOFC	45.7 (7.7)	57.8 (7.2)	38.14	**<.001**
IPC	41.9 (20.9)	54.6 (11.0)	7.82	**.007**
ITC	43.8 (7.6)	50.1 (7.9)	5.10	**.03**
rMFG	52.6 (7.6)	61.9 (8.1)	20.52	**<.001**

Means and SDs shown unless otherwise indicated.

Abbreviations: DRS-2 = Dementia Rating Scale – second edition; BPV = blood pressure variability; mOFC = medial orbital frontal cortex; IPC = inferior parietal cortex; ITC = inferior temporal cortex; rMFG = rostral medial frontal gyrus; CBF = cerebral blood flow