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RESEARCH ARTICLE

Association between low-frequency oscillations in blood pressure variability and brain age derived from neuroimaging

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Abstract

INTRODUCTION: We examined the association between low-frequency oscillations in blood pressure variability (LF-BPV) at baseline (past) and 12 years later (concurrent) and BrainAGE gap (an indicator of brain health).

METHODS: Participants were 110 adults (age range 37–83 years at baseline, 60% female) from the Midlife in the United States (MIDUS) study. LF-BPV (0.04–0.15 Hz) was spectrally decomposed from beat-to-beat BP waveforms acquired from finger photoplethysmography. BrainAGE was estimated using a Gaussian-process regression model applied to raw T1-weighted magnetic resonance imaging (MRI) scans. BrainAGE gap was calculated as brain age minus chronological age.

RESULTS: After adjustment for covariates, higher past diastolic LF-BPV was associated with significantly reduced BrainAGE gap ($\beta = -2.24$; 95% CI −4.15, −0.32, $p = 0.022$), as was higher concurrent diastolic LF-BPV ($\beta = -1.90$; 95% CI −3.68, −0.12, $p = 0.037$).

CONCLUSION: Our findings suggest that low-frequency oscillations in diastolic BPV are associated with slower brain aging relative to chronological age.

KEYWORDS
blood pressure, blood pressure variability, brain aging, MIDUS

Highlights

- Low-frequency oscillations in diastolic blood pressure variability, a marker of vasomotion, are reduced with aging.
- Low-frequency oscillations in diastolic blood pressure variability are favorably associated with BrainAGE gap, a marker of overall brain health, measured from neuroimaging.
- Reductions in vasomotion with aging may contribute to accelerated brain aging relative to chronological age.

1 | INTRODUCTION

Elevated blood pressure (BP) has a profound effect on the brain and contributes to cerebrovascular damage, cognitive impairment, and increased Alzheimer's disease and related dementia (ADRD) risk.[1] In addition to absolute (mean) BP levels, BP variability (BPV) also affects the brain in potentially countervailing ways depending on its magnitude and timescale.[2] Large variations in BP occurring over weeks, months, or even years are associated with cerebral small vessel disease and cognitive decline.[3,4] In contrast, very short-term BPV (heartbeat-to-beat fluctuations that occur within seconds to minutes) may be beneficial for brain health, although its effects are not well understood.

When very short-term BPV is spectrally decomposed in the frequency domain, a prominent oscillation can be detected within a low frequency (LF) bandwidth of 0.04–0.15 Hz. Currently, there are conflicting views on the (patho)physiological meaning of LF-BPV. Historically, LF-BPV was conceptualized as being of autonomic origin, reflecting sympathetic vasomotion.[5–8] Thus, higher LF-BPV was thought to indicate increased sympathetic vascular modulation and, by extension, increased vascular disease risk.[9] However, it has been suggested that vasomotion arising from low-frequency oscillations in hemodynamic variability may also have favorable physiological effects.[10,11] For example, induction of LF hemodynamic oscillations may protect tissue oxygenation in settings of reduced tissue perfusion.[12,13] Spontaneous LF hemodynamic oscillations may aid cerebrospinal fluid movement, glymphatic drainage, and perivascular debris clearance from the brain.[14–17] Relatedly, a recent scoping review based on nine studies that evaluated the relationship between very short-term BPV and neurocognitive function determined that six studies documented a positive association, two revealed no association, and only one noted an unfavorable effect.[18] More research is needed to advance our understanding of the relationship between LF-BPV and brain health.

Brain structure is well-known to change throughout the life course, with deviations from the typical brain aging trajectory (e.g., increased brain atrophy for a given age) reflecting latent neuropathological and neurodegenerative influences.[19] With the use of machine learning, a type of statistical analysis, thousands of tissue-specific brain features (e.g., cortical thickness, total and regional volumes of gray and white matter, cerebrospinal fluid) can be extracted from hundreds of magnetic resonance imaging (MRI) scans and used to 'learn' how patterns of data from the brain scans relate to chronological age.[20] Once these patterns are identified in healthy individuals, they can be applied to other individuals (who were not used in the original analyses) to predict their age. The deviation between this estimated brain age and the person's actual chronological age is known as the brain age gap. Several brain age calculators have been developed and proposed as biomarkers of biological aging and global brain health.[21] In this regard, advanced brain aging – a predicted brain age that is older than an individual's chronological age – has been associated with a higher risk for mild cognitive impairment and ADRD.[22]

RESEARCH IN CONTEXT

1. **Systematic review**: The authors relied on a traditional literature review, examining peer-reviewed publications from PubMed and Google Scholar. Keywords searched included, but were not limited to, "blood pressure variability", "brain age", and "neuroimaging". All studies utilized in our paper were deemed rigorous and of high quality. Brain age and brain age gap are relatively new areas of scholarship. While there are different methods available to estimate brain age, we chose to focus on one method that had a more robust literature linking it to clinical endpoints. Based on our search, brain age estimated from neuroimaging is emerging as a promising biomarker of brain health. The literature on blood pressure variability is complex, which we address in our paper. All relevant literature is cited appropriately.
2. **Interpretation**: While older literature suggests that very short-term blood pressure variability is a reflection of pathophysiology, newer literature supports that these oscillations benefit brain health. Therefore, our hypothesis that low-frequency oscillations in blood pressure variability would be favorably associated with brain age is based both on the totality of available literature and the evolution of this field.
3. **Future directions**: Based on findings, future studies are needed to elucidate the mechanisms by which low-frequency oscillations in blood pressure variability impact the brain. Additionally, future studies are needed to examine biobehavioral factors that may preserve very short-term blood pressure variability with aging as a potential strategy to maintain brain health.

The purpose of this study is to examine the association between LF-BPV and what we term the BrainAGE gap (i.e., the difference between brain age and chronological age) derived from structural (T1w) neuroimaging in middle-aged and older adults. By using the infrastructure of the Midlife in the United States (MIDUS) study, we are able to examine LF-BPV longitudinally and concurrently. This is important because past BP may be more strongly associated with brain structure and cerebral small vessel disease risk in older adults than concurrent BP,[23–25] and there is evidence that midlife BP is associated with brain white matter lesions, a marker of cerebral small vessel disease, and cortical atrophy later in life.[26–28] We hypothesize that higher LF-BPV, both past and concurrent, will be associated with slower brain aging relative to chronological aging. If this hypothesis is confirmed, this study will provide novel evidence of a favorable effect of LF oscillations in BPV on overall brain health and offer insight into the influence of the temporality and scale of hemodynamic fluctuations on brain aging.

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2 | METHODS

This study uses data from the MIDUS Biomarker and Neuroscience Projects conducted as part of the second (MIDUS 2, 2004–2009) and third (MIDUS 3, 2017–2022) waves of the MIDUS study. Beat-to-beat BP measures for the derivation of LF-BPV were completed as part of the Biomarker Project's Psychophysiology protocol at MIDUS 2 and MIDUS 3. Neuroimaging was completed in a subset of MIDUS 3 participants who completed the Psychophysiology protocol. MRI scans took place the day after participants completed the Psychophysiology protocol. Participants were excluded from the analytic sample if they did not complete the MRI study or did not complete the beat-to-beat BP testing at both MIDUS 2 and MIDUS 3. The final analytic sample includes 110 participants. All participants provided written informed consent, and the MIDUS study was approved by the University of Wisconsin-Madison Institutional Review Board (IRB) (IRB Protocol Number: Survey 2016-1051, Biomarker 2014-0813, Neuroscience MRI 2016-0054).

2.1 | BPV

For the M2 visit, participants stayed overnight in the clinical research center. They were given a light breakfast, no caffeine, and no alcohol, and they did not exercise before the measures. For the M3 visit, participants had the option to stay at a hotel. For those staying at a hotel, they were asked to adhere to the same guidelines as M2 (light breakfast, no caffeine, no alcohol, and no exercise). Visits were not standardized for the menstrual phase for regularly menstruating, premenopausal women. With participants seated, a finger cuff (Finapres Medical Systems, Amsterdam, Netherlands) was wrapped around the middle finger of their non-dominant hand. The hand was supported at heart level. Electrocardiograph (ECG) electrodes were placed on their left and right shoulders, as well as on their left lower quadrant. Data collection was initiated following a 1200-s habituation period (cuffs were adjusted, waveform calibration completed, participants may have moved around slightly, researchers conversed with participants), and a 240-s quiet rest period (no movement and no talking). The Physiocal feature was turned off for all measures. Beat-to-beat BP waveforms were recorded during an 11-min baseline (divided into two separate epochs of approximately 300 sec each).[29] For resting BP data, we chose the first epoch. Resting analog BP signals were digitized at 500 Hz by a 16-bit A/D conversion board (National Instruments, Austin, TX) and passed to a microcomputer. The BP waveforms were submitted to customized software that detected the time and magnitude of each systolic peak and diastolic trough, resulting in a BP time series.[29,30] Errors in marking systolic and diastolic values were identified via visual inspection by members of the MIDUS research team.[29] Values corresponding to ectopic beats were corrected by interpolation. LF-BPV (0.04–0.15 Hz) was computed based on 300-s epochs using an interval method for computing Fourier transforms similar to that described by DeBoer, Karemaker, and Strackee.[31,32] Before computing Fourier transforms, the mean of the BP series was subtracted from each value in the series to detrend the data. The series was filtered using a Hanning window, and the power over the LF band was summed. Estimates of spectral power were adjusted using the method of Harris to account for attenuation produced by this filter.[33] BPV data were computed during periods in which the respiratory rate was above the LF band (9 breaths/min), measured by a thoracic/abdominal stretch band that used the volume change to estimate a respiratory rate. The BPV was positively skewed rather than normally distributed (confirmed with Shapiro–Wilk and Kolmogorov–Smirnov tests). Therefore, we used the logarithmically transformed (natural logarithm [ln]) LF-BPV variables provided in the MIDUS dataset in our analyses. We examined both systolic and diastolic LF-BPV.

2.2 | Neuroimaging and BrainageR pipeline

All structural scans were acquired using a 3T scanner (MR750, GE Healthcare, Waukesha, WI) with a 32-channel NOVA head coil. These data were derived from BRAVO T1-weighted (T1w) structural images with 1 mm^3 isotropic voxels (repetition time [TR] repetition time = 8.2 ms, echo time [TE] echo time = 3.2 ms, flip angle = 12°, matrix = 256 × 256, field of view [FOV] = 256 mm, slices = 160, slice thickness = 1 mm, and inversion time = 450 ms, total duration = 7.5 min).

BrainAGE was estimated using brainageR v2.0 (https://github.com/james-cole/brainageR/releases/tag/2.0). The first step of the brainageR algorithm segments the T1w scans into gray matter and white matter, which are normalized to standard space using non-linear spatial registration. The two brain segmentation images are then concentrated and converted into a similarity matrix. Gaussian-process regression models are then used to predict chronological age. The voxel-wise pipeline was previously trained on 2001 research participants without neurological disorders, psychiatric disorders, head trauma, and/or other medical illnesses (age range 18–90 years). Using a cross-validation approach, brain age estimates from this pipeline accounted for 88% of the variance in chronological age, with a mean absolute error (MAE) of 5.02 and a root mean square error (RMSE) of 6.31. BrainageR is freely available for use (https://github.com/james-cole/brainageR; https://doi.org/10.5281/zenodo.3476365), and v2.0 was applied to the MIDUS Neuroscience sample's BRAVO T1-weighted structural images to compute each individual's BrainAGE. The brainageR algorithm has high accuracy and test-retest reliability compared to other brain age gap algorithms.[34] BrainAGE gap was calculated as estimated BrainAGE minus self-reported chronological age. A positive value signifies accelerated brain aging relative to chronological age, while a negative value signifies slower brain aging relative to chronological age.

2.3 | Analytic plan

We use multivariable linear regression to assess the association of past (MIDUS 2) and concurrent (MIDUS 3) LF-BPV with BrainAGE gap measured at MIDUS 3. When building our model, we explored a range of factors that may affect brain aging, including: sociodemographic variables (age, sex, race, education, household income); health behaviors and related factors (tobacco use, alcohol use, physical activity, body mass index [BMI]); chronic disease status (history of heart disease, diabetes mellitus, stroke/transient ischemic attack [TIA], high cholesterol, high BP); and medication use (cardiovascular agents including BP medications, central nervous system agents, metabolic agents, hormonal agents). Variables were entered into the model if they demonstrated a univariate association with the dependent variable at $p \leq 0.10$. We additionally forced sex and race into the model as we view these factors as important constructs to consider when exploring brain aging. Self-reported chronological age was included in the model because BrainAGE calculated from the method used herein may overestimate brain age for younger adults and underestimate brain age for older adults.[35–38] For the regression analysis, chronological age was centered by subtracting the mean age from each participant's self-reported age. When examining associations between LF-BPV at MIDUS 2 with BrainAGE gap at MIDUS 3, we forced a time-lag variable into the model to account for different lengths of time between baseline BPV measures and subsequent neuroimaging (mean time lag 12 ± 2 years). Finally, mean (absolute) BP was forced into models so that we could estimate the association of LF-BPV with BrainAGE gap independent of the influence of mean BP on BrainAGE gap. Analyses were completed separately for systolic BPV and diastolic BPV. In the systolic BPV analyses, we control for mean systolic BP. In the diastolic BPV analyses, we control for mean diastolic BP. Paired sample *t*-tests were used to compare continuous variables (from MIDUS 2 to MIDUS 3), while categorical variables were compared with Fisher's exact test. All analyses were carried out using SPSS v. 29 (IBM), and significance was set a priori at $p < 0.05$.

3 | RESULTS

Our sample included 110 middle-aged and older adults. Descriptive characteristics across time points are presented in Table 1. Participants were mostly female (60%), non-Hispanic White (68%) individuals and had an educational attainment of: 27.3% high school or less, 28.2% some college or technical training, and 44.5% Bachelor's degree or more. Based on BMI at MIDUS 2, 45% were categorized as obese (BMI ≥ 30 kg/m^2) and 31% as overweight (BMI 25–30 kg/m^2). At MIDUS 3, the overall MIDUS sample who completed the Survey Project was N = 3683 participants, with a mean age = 63.37 (SD = 11.30) years, and an age range of 39–93 years. The overall sample was 56% Female and 80.5% White. The educational attainment distribution was: 31% high school or less, 30.1% some college or technical training, and 38.9% Bachelor's degree or more. The subsample used in our analyses is slightly younger on average and more educated than the full MIDUS 3 Survey sample. However, our analytic subsample includes a 43-year age range and a significant percentage of people with a high school education or less. Finally, our analytic subsample has a slightly higher percentage of female participants, and a greater percentage of people who self-identify as Black and/or African American, Asian, Native American, and Alaska Native.

While 17% had positive BrainAGE gap values, the mean BrainAGE gap in the sample was −6.8 years (median = −6.1 years), which indicates slower brain aging than chronological aging for the sample as a whole. Values for BrainAGE gap in the sample were comparable to those reported in the literature.[19,39] While no normative data exist for measures of BPV, the range of values observed in our sample (Table 1) closely approximates the range of values previously reported in the larger MIDUS cohort (N = 2118).[29]

From MIDUS 2 to MIDUS 3, there were increases in household income, BMI, and the proportion of participants who reported a history of stroke/TIA, diabetes mellitus, and high BP ($p < 0.05$). However, none of these variables or the other health behaviors and conditions that we considered for inclusion were associated with BrainAGE gap at $p \leq 0.10$. Therefore, none of those variables were included in the multivariable model we estimated. While there was no significant change in diastolic BP across time points, there was a significant reduction in diastolic (ln) LF-BPV from MIDUS 2 to MIDUS 3 ($p < 0.05$). Conversely, while there was an increase in systolic BP across time points ($p < 0.05$), there was no change in systolic (ln) LF-BPV from MIDUS 2 to MIDUS 3.

Supplementary (online) Table S1 displays data for each of the regressors in our model along with full model statistics. Table 2 displays the results from separate multiple linear regression analyses. There was one statistical outlier for diastolic LF-BPV at MIDUS 2 and MIDUS 3. Excluding these participants did not affect results, so they were retained in the final model. Past systolic (ln) LF-BPV at MIDUS 2, concurrent systolic (ln) LF-BPV at MIDUS 3, or change in systolic (ln) LF-BPV from MIDUS 2 to MIDUS 3 were not associated with BrainAGE gap. Diastolic (ln) LF-BPV at both MIDUS 2 (past) and MIDUS 3 (concurrent) was significantly associated with BrainAGE gap in a model that controlled statistically for age, sex, race, education, diastolic BP, and time lag (for the MIDUS 2 analysis only). Figure 1A,B display the partial regression plots for diastolic LF-BPV as the independent variable and brain age gap as the dependent variable for MIDUS 2 and MIDUS 3, respectively. In each model we estimated, the constant was negative, which is indicative of a lower brain age than chronological age. For each unit increase in (ln) LF-BPV, there was an approximate 2-year reduction in brain age relative to chronological age (i.e., the BrainAGE gap became more negative). To put this in perspective, we used the relevant equation to obtain the predicted BrainAGE gaps for someone with +1 standard deviation above the mean LF-BPV and -1 standard deviation below the mean LF-BPV, and the reference-category characteristics for the other variables in the model (i.e., we just used the constant and coefficient for LF-BPV given in Table 2 to generate the predicted values). For the past equation, the predicted BrainAGE gaps are 7.9 and 11.8 years; for the concurrent equation, the predicted BrainAGE gaps are 7.1 and 10.6 years. The association between change in diastolic (ln) LF-BPV from MIDUS 2 to MIDUS 3 and BrainAGE gap approached but did not reach statistical significance ($p = 0.066$).

According to respiration measures acquired during the BP measurement, three participants had a respiratory rate of 8 breaths/min, two participants during baseline (M2) measures, and one participant

TABLE 1 Descriptive characteristics, health behaviors, and blood pressure over time.

n = 110	MIDUS 2 2004–2009	MIDUS 3 2017–2022	*p*-value
Age, years (range)	52 ± 9 (37–83)	64 ± 9 (48–95)	<0.001
Female sex, n (%)	66 (60%)		–
Race, n (%)			–
White	76 (68%)	–	
Black/African American	30 (27%)	–	
Asian	2 (2%)	–	
Native American/Alaskan	2 (2%)	–	
Education, n (%)			–
4-year college degree or higher	50 (45%)	–	
Some college education,	30 (27%)	–	
High school/GED or less	30 (27%)	–	
Household income, dollars	67443 ± 54252	91977 ± 106738	0.020
Brain age gap, years	–	−6.8 ± 8.5	–
Body mass index, kg/m^2	30 ± 6	31 ± 6	0.001
Systolic BP, mmHg	123 ± 19	129 ± 22	0.010
Systolic (ln) LF-BPV, mmHg^2	2.27 ± 0.87	2.16 ± 0.91	0.291
Diastolic BP, mmHg	61 ± 12	63 ± 12	0.178
Diastolic (ln) LF-BPV, mmHg^2	1.06 ± 0.86	0.71 ± 0.88	<0.001
Hx heart disease, n (%)	4 (4%)	5 (5%)	0.999
Hx stroke/TIA, n (%)	2 (2%)	6 (5%)	0.045
Hx diabetes mellitus, n (%)	14 (13%)	23 (21%)	0.012
Hx high cholesterol, n (%)	49 (45%)	55 (50%)	0.241
Hx high blood pressure, n (%)	36 (33%)	50 (45%)	0.001
Hormone medication, n (%)	20 (18%)	24 (22%)	0.286
Hx smoking, n (%)	47 (43%)	49 (45%)	0.417
Alcohol use, days/week	1.5 ± 1.4	1.7 ± 1.8	0.043
Physical activity, n (%)	83 (75%)	73 (66%)	0.105

Note: Results are displayed as mean ± SD for continuous variables unless otherwise indicated as number and percentage (n, %).
Abbreviations: BP, blood pressure; GED, General Education Development; Hx, history; LF-BPV, low-frequency blood pressure variability; MIDUS, Midlife in the United States; TIA, transient ischemic attack.

TABLE 2 Association between LF-BPV and brain age gap.

				95% Confidence interval	
Parameter	(Constant)	β	Standard error	Lower bound	Upper bound
Diastolic LF-BPV (M2)	−4.81	−2.24	0.97	−4.15	−0.32
Diastolic LF-BPV (M3)	−4.78	−1.90	0.90	−3.68	−0.12
Δ Diastolic LF-BPV	−3.72	−1.70	0.92	−3.52	0.12
Systolic LF-BPV (M2)	−1.41	−1.78	0.92	−3.54	0.10
Systolic LF-BPV (M3)	−5.19	−1.09	0.88	−2.84	0.65
Δ Systolic LF-BPV	−0.20	−0.72	0.91	−2.53	1.09

Notes: For M2 analyses, models were adjusted for centered age at M2, sex, race, education, and time lag between M2 and M3. For M3 analyses, models were adjusted for centered age at M3, sex, race, and education. For models examining diastolic LF-BPV, we additionally entered mean diastolic BP at the respective time point. For models examining systolic LF-BPV, we additionally entered mean systolic BP at the respective time point. For our change (Δ) models, we included centered age at M2, sex, race, education, mean BP at M2, and either diastolic or systolic LF-BPV at M2.
Abbreviations: LF-BPV, low-frequency blood pressure variability; M2, MIDUS 2; M3, MIDUS 3; MIDUS, Midlife in the United States.

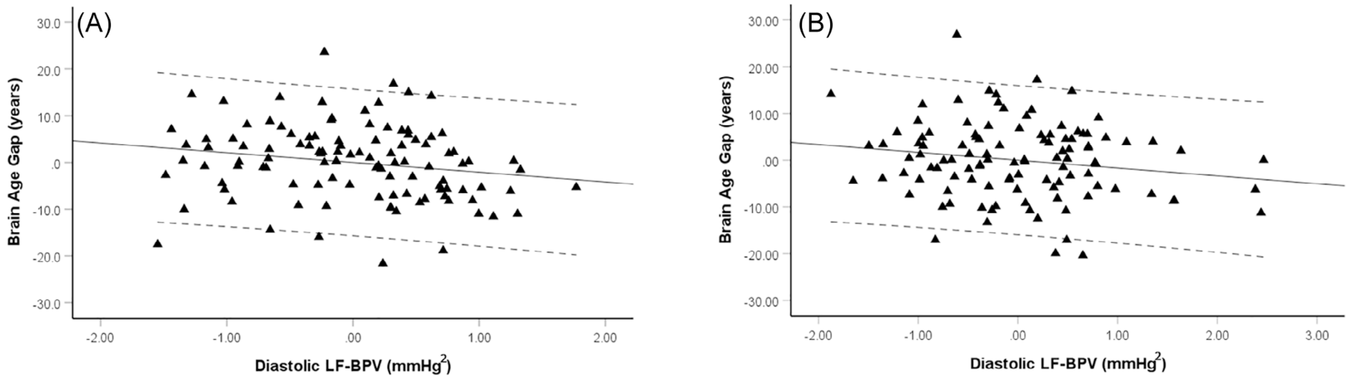

FIGURE 1 Partial regression plots for (A) diastolic LF-BPV at MIDUS 2 and (B) diastolic LF-BPV at MIDUS 3 with brain age gap (brain age minus chronological age), controlling for covariates. The dark line represents the slope of the partial regression line, while the dashed lines demarcate the individual 95% confidence band. LF-BPV, low-frequency blood pressure variability; MIDUS, Midlife in the United States.

during M3 measures. All other participants had a respiratory rate > 9 breaths/min. Sensitivity analyses were conducted, excluding these participants, and results were not affected, so all participants were retained in the final analyses.

4 | DISCUSSION

A positive brain age gap (i.e., when brain age exceeds chronological age) is thought to reflect an accumulation of aberrant age-related changes to the brain.[21] Relatively high brain age is associated with cognitive decline, the transition from mild cognitive impairment to dementia, and markers of underlying ADRD pathology (amyloid and tau).[39–44] Brain age is also an independent predictor of cerebrovascular disease burden and mortality.[19,45–47] We examined the association between LF oscillations in BPV and BrainAGE gap in a sample of 110 middle-aged and older adult participants in the MIDUS study. Overall, our findings suggest a favorable association between diastolic LF-BPV (past and concurrent) and global brain health, measured as BrainAGE gap.

While the absolute pressures measured in the finger and brain (intracranial pressure) may not be the same, LF oscillations (0.1 Hz) that occur over short timescales in the finger and the brain are associated and may reflect similar underlying physiologies. Similar LF oscillations are seen across the systemic circulation, occurring in the renal circulation,[48,49] omental circulation,[50] skeletal muscle microcirculation,[51] cutaneous circulation,[52,53] and retinal circulation.[54] LF hemodynamic oscillations measured in the periphery (operationally defined as oscillations in pressure measured via pulse decomposition, pulse volume plethysmography, and oxyhemoglobin from near-infrared spectroscopy [NIRS]) correlate with brain LF oscillations in the blood oxygenation level dependent (BOLD) signal measured with functional MRI (fMRI) and magnetic resonance encephalography (MREG).[55–60] Brain BOLD signal fluctuations specifically within the default-mode and the visual networks have similar spectral density distributions to the fluctuations of systemic BP and cerebral blood flow velocity measured from the middle cerebral artery.[61] Mathematical modeling further suggests that fluctuations in systemic BPV account for 60% of the variance in cerebral blood flow fluctuations captured in the middle cerebral artery.[62] This is important because it is the changes in cerebral flow variability within the LF range (both spontaneous and induced) that impact brain tissue oxygenation.[2,10] Specifically, oscillatory blood flow produced by vasomotion may achieve better tissue oxygenation than that obtained from a steady flow of blood.[63,64] Additionally, upstream cerebral arterial pressure and blood flow fluctuations transmitted into the cerebral microcirculation play an important role in neurovascular coupling and preventing brain Aβ deposition.[17] Hemodynamic oscillations occurring within the same frequency range as vasomotion (0.1 Hz) are coupled to neuronal activity.[60,65,66] Vasomotion has also been theorized to contribute to the driving force of solute clearance from the brain.[16,17,67] Relatedly, loss of LF hemodynamic oscillations has been linked to ADRD pathology.[68–70] Low LF-BPV may thus impact and/or reflect changes in cerebrovascular function and perfusion, important modulators of neuroinflammation, neurovascular coupling, white matter structure, and Aβ clearance. Over time, reductions in LF-BPV would be expected to hasten global brain aging.[71,72]

The coupling between BPV and cerebral blood flow variability largely informs the measurement of dynamic cerebral autoregulation.[73] Cerebral autoregulation is an essential intrinsic physiological mechanism that describes the ability of cerebral blood vessels to dilate or constrict to maintain perfusion in the presence of fluctuations in BP. Preclinical data have demonstrated that even mild impairment of cerebral autoregulation may lead to neurodegeneration and dementia in older adults.[74–77] Impaired cerebral autoregulation could lead to decreases in perfusion pressure during hypotensive perturbations, causing neuronal hypoperfusion. Impaired cerebral autoregulation could also lead to increased perfusion pressure during hypertensive challenges, transmitting excess pressure pulsatility to downstream capillaries, which can contribute to disruption of capillary integrity and blood-brain barrier breakdown.[78] An additional physiological mechanism that can protect the brain from large fluctuations in BP within the cerebral arteries is vascular compliance. Vascular stiffening and the concomitant loss of cerebral vascular capacitance may attenuate the transmission of LF hemodynamic oscillations into the brain.[79] A stiffer/less compliant vasculature may contribute to/be caused by a blunted vascular reactivity from endothelial and vascular smooth muscle dysfunction that detrimentally impacts vasomotion and hastens brain aging.[80,81] More research is needed to examine the interaction of cerebral autoregulation and arterial compliance on brain aging.

Several potential mechanisms have been suggested to explain the genesis of vasomotor activity corresponding to LF-BPV, including: sympathetic-autonomic modulation/resonance within the baroreflex arc (Mayer waves); intrinsic vascular myogenic tone (calcium and voltage-dependent cell membrane oscillator); and a central neurogenic oscillator.[5–8] Each of these potential mechanisms may, in turn, interact with other systemic hemodynamic factors to uniquely affect beat-to-beat fluctuations in systolic or diastolic pressure. For example, the interaction of beat-to-beat variations in large artery stiffness[82] with stroke volume[83] would be expected to affect systolic BP variability more than diastolic BP variability. Conversely, diastolic BP variability may be more affected by such factors as: variation in diastolic decay from beat-to-beat changes in heart rate; microvascular tone affecting peripheral vascular resistance and diastolic runoff; and regional compliance (Windkessel/reservoir function) affecting diastolic recoil.[84] As the diastolic phase of the cardiac cycle lasts longer than the systolic phase, the brain may be more sensitive to diastolic BPV and related systemic hemodynamic-vascular factors (microvascular dysfunction, vascular compliance) compared with systolic BPV.

We observed a longitudinal reduction in diastolic LF-BPV with chronological aging, spanning approximately 12 years. This is consistent with previous cross-sectional reports of lower diastolic LF-BPV in older adults compared with younger adults[85–87] and an inverse association between age and diastolic LF-BPV.[29] Aging is associated with physiological changes that could contribute to the observed reduction in diastolic LF-BPV, including reductions in baroreceptor sensitivity, microvascular/endothelial function, vascular compliance, and myogenic tone. Our findings further suggest that systolic LF-BPV, when measured in the seated position, may not change as much with aging. Compared to the supine position, the seated position may augment sympathetic activity,[88] potentially differentially impacting systolic and diastolic BPV. When BPV is assessed in the time domain as the standard deviation or the variation independent of mean, high systolic BPV is associated with several metrics of ADRD risk, including lower cerebrovascular reactivity, cortical atrophy, circulating amyloid and tau, and lower functional connectivity.[89–92] Our results suggest that findings obtained when BPV is assessed in the frequency domain are not equivalent to those garnered from time-domain measures. Many time-domain metrics of BPV are inherently centered around the cardiac frequency, as the variability is derived from beat-to-beat measurements. As such, differences between frequency-domain and time-domain metrics may be due to differences in the frequency of the variability.

Limitations of this study should be noted and addressed in future research. The nature of the MIDUS Neuroscience in-person data collection requires study participants to travel to the University of Wisconsin-Madison, which means that only those physically and cognitively healthy enough to travel, often by air or bus, participate in the multiple days of research activities (including MR neuroimaging). As such, these participants may reflect a healthier-than-average group. However, our sub-sample still has a considerable range in health as reflected by the BPV measures and range in BrainAGE gap. In analyzing both systolic and diastolic BPV at two time points and their change, we acknowledge the increased possibility of detecting significant effects by chance due to multiple comparisons (6 in total). Although these tests were grounded in relevant hypotheses, some of the observed p-values might not reflect genuine effects. If we applied a Bonferroni adjustment to our findings and set significance at $p < 0.008$, our findings would not be retained and, as such, should be interpreted with caution. We view findings as hypothesis-generating. We did not assess cerebral blood flow variability or cerebral tissue oxygenation; thus, we cannot confirm that changes in LF oscillations in BPV measured in the finger are truly representative of direct cerebral hemodynamic effects. In many studies that examine LF hemodynamic oscillations in the literature, measures commonly focus on mean arterial pressure LF oscillations. MIDUS did not calculate LF oscillations in mean arterial pressure; only systolic and diastolic pressures. Considering that the cardiac cycle comprises approximately 1/3 time spent in systole and 2/3 time in diastole (with the form factor changing with age), the effects of mean pressure oscillations previously noted may be detecting the larger diastolic contribution. We also did not have a measure of BrainAGE gap at our baseline time point (M2), given the limited imaging at M2. With continued neuroimaging being performed in upcoming MIDUS waves, future studies can leverage the longitudinal study design of MIDUS to examine how change in BPV over time correlates with changes in brain aging over time. Another limitation is that laboratory visits for the assessment of BPV were not standardized for menstrual cycle phase among premenopausal female participants. Menstrual cycle affects sympathetic activity and baroreflex sensitivity,[93] potential modulators of vasomotion and LF oscillations in BPV. Because MIDUS does not have measures of vascular function (arterial stiffness), hypotheses on mechanisms responsible for differential associations between systolic and diastolic BPV and BrainAGE gap cannot be tested. Finally, this study did not explore the impact of adverse childhood or lifetime experiences on BPV and BrainAGE gap. Childhood maltreatment is associated with cerebral and systemic vascular dysfunction[94] and accelerated brain aging in adulthood.[95] Future studies are needed to further examine biobehavioral and socioenvironmental determinants of BPV and potential consequences on brain aging.

In conclusion, higher diastolic LF-BPV is associated with attenuated brain aging in middle-aged and older adults. Chronological aging is associated with reductions in LF-BPV, which may have detrimental implications for brain aging. Future research is needed to examine if interventions that preserve diastolic LF-BPV with aging have favorable effects on long-term brain health.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

All participants provided written informed consent, and the MIDUS study was approved by the University of Wisconsin-Madison IRB.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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