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Original Article

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Dynamical Regulation of Blood Pressure and Cognitive Function

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BACKGROUND: Blood pressure (BP) is not steady. It varies over intervals from months to consecutive cardiac cycles, and this variation contains meaningful information beyond mean BP. Variability over multiple clinic visits (VVV-BP) and during 24-h ambulatory monitoring (ABPV) is positively related to risk of stroke and coronary artery disease and negatively associated with cognitive performance. Beat-to-beat BP variation, often quantified as low frequency variability (0.04–0.15 Hz, LF-BPV), is less well-studied. Here, we examine the relationship between LF-BPV and cognitive outcomes in 1953 participants from the Midlife in the US study.

METHODS: Participants completed the Brief Test of Adult Cognition by Telephone from which we derived episodic memory (EMF) and executive function (EFF) factors and a composite index. With participants in the seated position, the continuous BP signal was recorded noninvasively with a Finometer. The resultant time series was submitted to Fourier-based spectral analysis to compute LF-BPV. Linear regression models estimated the associations with cognitive indices.

RESULTS: Systolic (LF-SBPV) and diastolic (LF-DBPV) were positively associated with EFF ($b = 0.073 \pm 0.033$, $P = 0.02$), EMF ($b = 0.079 \pm 0.036$, $P = 0.04$), and the composite index ($b = 0.101 \pm 0.035$, $P = 0.004$) after adjustment for age, sex, education, and income. Findings were similar for LF-DBPV.

CONCLUSIONS: This positive association is consistent with evidence demonstrating that LF blood pressure variability contributes to increased delivery of oxygenated blood to the brain and clearance of metabolic and cellular waste via the brain's glymphatic system and intramural periarterial drainage pathway, both of which contribute to superior cognitive performance.

Keywords: blood pressure; blood pressure variability; cognitive function; hypertension; observational study.

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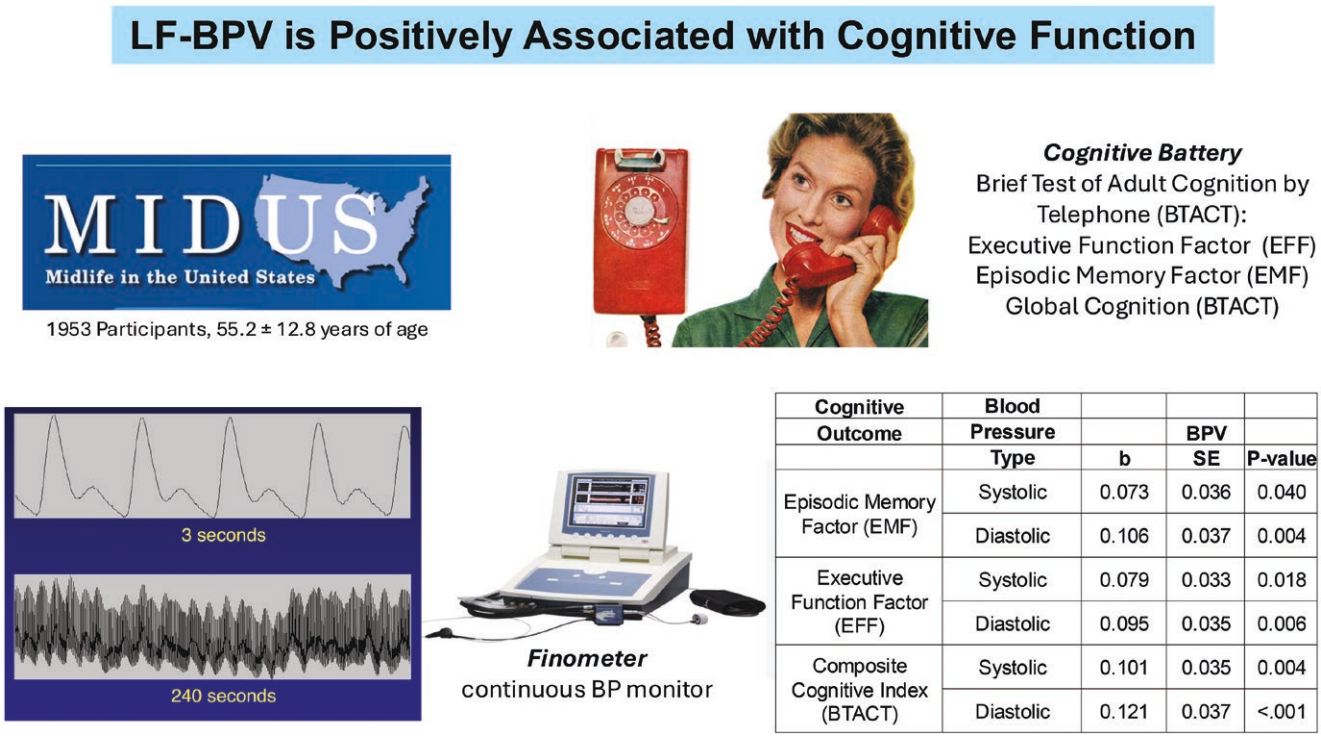
Graphical Abstract



Cognitive Outcome	Blood Pressure Type	b	BPV SE	P-value
Episodic Memory Factor (EMF)	Systolic	0.073	0.036	0.040
	Diastolic	0.106	0.037	0.004
Executive Function Factor (EFF)	Systolic	0.079	0.033	0.018
	Diastolic	0.095	0.035	0.006
Composite Cognitive Index (BTACT)	Systolic	0.101	0.035	0.004
	Diastolic	0.121	0.037	<.001

The link between elevated blood pressure (BP) and increased risk for many conditions, including stroke, myocardial infarction, renal disease,[1] and impaired cognitive function[2] is well-established. However, BP is not static. It is dynamic and undergoes a significant degree of variation continuously. Current approaches to medical management attempt to control for this "noise" by averaging multiple measurements but recent evidence shows that this blood pressure variability (BPV) contains meaningful information. Findings depend upon how BPV is measured: (i) repeatedly over weeks or even years (visit-to-visit variability [VVV-BP]); (ii) on a 24-h scale by ambulatory monitoring (ABPV); and (iii) on a beat-to-beat basis.

In 16,758 participants free of dementia at study entry and followed for 2 years,[3] in 3,319 noninstitutionalized patients age ≥65 years followed for 3 years,[4] and in 7.8M participants without dementia followed for 6.2 years,[5] VVV-BP was directly related to poorer cognition and elevated risk of dementia independent of mean SBP and DBP. Measured over a range of 15 min to 1-h intervals over 24 hours, greater ABPV was related to poorer cognitive function in 202 and 232 patients (mean age = 82 years).[6,7]

Fewer studies assess beat-to-beat BPV largely because noninvasive acquisition of the continuous BP signal, the input for analyses of beat-to-beat BPV, requires expensive and complex devices, e.g., the Finometer (Finapres Medical Systems, Amsterdam), limiting collection of these data. However, the technology for monitoring the continuous BP waveform is evolving rapidly, making acquisition of LF-BPV increasingly feasible.

Further complicating matters, a variety of metrics have been used to measure beat-to-beat BPV: time domain statistics such as SD are indices of *total* variability while frequency domain measures parse BPV into discrete frequency bands, e.g., low (LF, 0.04–0.15 Hz) and high (HF, 0.15–0.40 Hz) frequency variation, that may be selectively sensitive to underlying physiology and clinically significant events not captured by total BPV. Beat-to-beat BPV is also expressed as "pulsatility," a high frequency (~1.0 Hz) index, and "vasomotion" at lower frequencies (0.04–0.15 Hz). Reports of associations between BPV and cognitive function differ depending upon the BPV metric.

HF-BPV is not commonly measured, largely because its physiological significance is limited: it is widely recognized to be the product of respiration-induced changes in intrathoracic pressure which occur in the 0.15–0.40 Hz frequency band. Pulsatility generally refers to BPV deriving from each cardiac cycle, i.e., at the heart rate. As such, HF-BPV and pulsatility are different from each other but importantly, each is different from LF-BPV.

To our knowledge, only one study reports on associations between frequency domain indices of BPV and cognitive function in a community study: in 1,140 individuals, cognitive impairment measured by the MoCA was positively associated with HF-SBPV but not with LF-SBPV.[8] Here we report findings on the relationship between LF-BPV and multiple domains of cognitive function across a large, diverse sample of participants from the NIA-sponsored Midlife in the US (MIDUS) study.

METHODS

Participants

MIDUS is a nationally representative study of role of behavioral, psychological, and social factors in age-related variations in health and well-being. Data came from MIDUS2 (2004–2009, $N = 5,555$) and the MIDUS Refresher (MIDUSR, 2011–2015, $N = 4,085$), each with a survey plus projects measuring cognitive function and biomarkers.[9] Institutional Review Board approval was obtained for all MIDUS data collection and participants provided informed consent.

Measurement of cognitive function

The Brief Test of Adult Cognition by Telephone (BTACT) battery is a reliable, validated measure of cognition[10] including measures of processing speed, reaction time, and task-switching/inhibitory control. Exploratory and confirmatory factor analyses identified episodic memory (EMF) and executive functioning (EFF) factors.[10] Tests were standardized using z-scores and the mean of the tests loading on the respective factors was computed to create factor scores. The two-factor scores were then standardized to z-scores. A BTACT composite score was computed as the average of the standardized values for all cognitive tests.[10]

Measurement of beat-to-beat BPV

In the Biomarker project, participants traveled to one of three clinical research centers (Wisconsin, UCLA, Georgetown) for a 1.5-day visit. During a morning session, they received a light breakfast without caffeinated beverages, then were fitted with ECG electrodes and respiration bands. A monitoring cuff from a Finometer beat-to-beat BP monitor was placed on the middle finger of the nondominant hand for continuous BP monitoring for an 11-minute quiet, resting baseline period.

The continuous BP and ECG waveforms were sampled at 500 Hz using a National Instruments 16-bit A/D board, and along with respiration signals, were collected on a microcomputer. Systolic peaks and diastolic troughs were identified using custom-written software, producing SBP and DBP time series that were reviewed for artifact and if possible, corrected by linear interpolation. The first 300s epoch without missing or implausible data was then identified, LF-BPV (0.04–0.15 Hz) was computed, using an interval method for computing Fourier transforms similar to that described by DeBoer et al.[11] Prior to computation of Fourier transforms, the mean of each BP series was subtracted from each value in the series. A Hanning window[12] was applied to the time series and power over the LF band was summed and adjusted to account for attenuation produced by this window. LF-BPV was averaged across the two 300-sec epochs.

Statistical analysis

All variables were examined for normality and outliers. To address large outliers and general right skew in LF-SBPV and -DBPV values, a natural-log transformation was applied. Demographic, physiological, and cognitive characteristics were summarized with means and standard deviations, and medians and interquartile ranges for continuous variables, or with frequencies and proportions for categorical variables.

Linear regression models were used to estimate the association between LF-BPV and Episodic Memory (EMF), Executive Function (EFF), and BTACT Composite scores for the entire sample ($N = 1,953$). The first model controlled only for BP, then sociodemographic variables were added one at a time (age [as categorical; younger (25–49), middle-aged (50–64), older (65–86)], sex, education, and income), adjusting for multiple sociodemographic variables.

In a sensitivity analysis, we repeated these analyses only in participants whose physiological and cognitive assessments were within 18 months of one another. Finally, to see if any of these associations changed over time, analyses were repeated, adding the interactions between the time between physiological and cognitive visits and BPV and BP.

All analyses were conducted using SAS version 9.4, with two-sided tests and a preselected level of significance 5%.

RESULTS

In MIDUS2, there were 4,512 and 1,255 participants and in MIDUSR, 2,763 and 863 participants, respectively, in the cognitive and biomarker projects. Of these, 1,152 MIDUS2 and 801 MIDUSR (1,953 in total) participants had complete cognitive and biomarker data. Missing data were due to equipment failures, inability or unwillingness to participate in the psychophysiology study, or missing cognitive scores.

Table 1 presents the sociodemographic and clinical characteristics of the participants. The mean age was 55.2 ± 12.8 years old, with slightly more women than men (54.6% vs. 45.4%). 47.6% had a bachelor's degree or higher; 29.8% completed at least some college, and 22.6% had a high school diploma, GED, or less. Of participants who disclosed their income, 15.9% earned below 200% of the Federal Poverty Level, 23.3% earned between 200% and 400%, 23.4% made between 400% and 600%, and 37.4% made over 600% of that level. The mean ± SD of SBP and LF-SBPV were 123.6 ± 18.2 mmHg and 13.6 ± 12.9 mmHg,[2] while the mean DBP & LF-DBPV were 61.7 ± 11.5 mmHg and 4.0 ± 3.4 mmHg.[2] The mean ± SD values for EMF, EFF, and the BTACT composite were 0.1 ± 0.9, 0.1 ± 0.9, and 0.1 ± 1.0, respectively.

Table 2 presents the regression models for the entire sample ($N = 1,953$), where the mean interval between the physiological and cognitive assessments was 21.4 ± 12.0 months. When adjusting only for SBP, LF-SBPV was positively associated with EMF ($b = 0.076$, SE = 0.029, $P = 0.009$), EFF ($b = 0.141$, SE = 0.028, $P < 0.001$), and BTACT ($b = 0.161$, SE = 0.03, $P < 0.001$). Similarly, when adjusting for only DBP, LF-DBPV was positively associated with EMF ($b = 0.16$, SE = 0.029, $P < 0.001$), EFF ($b = 0.235$, SE = 0.028, $P < 0.001$), and BTACT ($b = 0.266$, SE = 0.029, $P < 0.001$). **Figure 1** depicts these findings.

These associations remained statistically significant when adjusting for each sociodemographic variable separately, except for the association between LF-SBPV and EMF, which no longer remained significant with age ($b = 0.044$, SE = 0.028, $P = 0.127$) or income level ($b = 0.061$, SE = 0.039, $P = 0.118$) in the model.

After adjusting for age, sex, education, income, and BP, LF-SBPV, and LF-DBPV remained positively associated with EMF (LF-SBPV: $b = 0.073$, SE = 0.036, $P = 0.04$; LF-DBPV: $b = 0.106$, SE = 0.037, $P = 0.004$), EFF ($b = 0.079$, SE = 0.033, $P = 0.018$; $b = 0.095$, SE = 0.035, $P < 0.006$), and BTACT ($b = 0.101$, SE = 0.035, $P < 0.004$; $b = 0.121$, SE = 0.037, $P < 0.001$).

Table 3 presents the results of the sensitivity analyses ($N = 885$), where the average interval between assessments was 11.1 ± 3.6 months. When adjusting only for SBP, LF-SBPV was positively associated with EFF ($b = 0.105$, SE = 0.042, $P = 0.014$) and BTACT ($b = 0.114$, SE = 0.044, $P = 0.01$), while LF-DBPV, when adjusted for DBP, was positively associated with all cognitive outcomes—EMF ($b = 0.15$, SE = 0.045, $P = 0.026$), EFF ($b = 0.186$, SE = 0.042, $P < 0.001$), and BTACT ($b = 0.214$, SE = 0.044, $P < 0.001$). In multivariable analyses adjusting for age, sex, education, and income, the associations between LF-SBPV and EFF ($b = 0.127$, SE = 0.049, $P = 0.01$) and BTACT ($b = 0.129$, SE = 0.052, $P = 0.013$) and between LF-DBPV and EFF ($b = 0.131$, SE = 0.051, $P = 0.011$), and BTACT ($b = 0.144$, SE = 0.053, $P = 0.007$) remained significant.

None of the interactions between time and SBP, LF-SBPV, DBP, or LF-DBPV was statistically significant, indicating no significant changes in the associations of BP or BPV with cognitive outcomes over time.

Table 1. Demographic, physiological, and cognitive characteristics of participants

Variable	*n*	Overall (*N* = 1,953)
Age, years	1,953	
Mean ± SD		55.2 ± 12.8
Median (IQR)		55.0 (46.0–64.0)
Age (categorized)	1,953	
Younger (25–49)		665 (34.1%)
Middle-Aged (50–64)		817 (41.8%)
Older (65–86)		471 (24.1%)
Sex	1,953	
Male		886 (45.4%)
Female		1,067 (54.6%)
Race	1,953	
White		1,535 (78.6%)
Black/African-American		283 (14.5%)
Other		135 (6.9%)
Education	1,949	
HS/GED or less		441 (22.6%)
AA degree/some college		580 (29.8%)
BA degree or higher		928 (47.6%)
Income (Ratio to Federal Poverty Level)	997	
<200% FPL		159 (15.9%)
200–<400% FPL		232 (23.3%)
400–<600% FPL		233 (23.4%)
>= 600% FPL		373 (37.4%)
Physiological characteristics		
Systolic blood pressure (mmHg)	1,670	
Mean ± SD		123.6 ± 18.2
Median (IQR)		122.3 (111.0–135.0)
Systolic blood pressure variability (mmHg2)	1,670	
Mean ± SD		13.6 ± 12.9
Median (IQR)		10.3 (6.0–17.3)
Diastolic blood pressure (mmHg)	1,670	
Mean ± SD		61.7 ± 11.5
Median (IQR)		61.5 (54.2–68.8)
Diastolic blood pressure variability (mmHg2)	1,670	
Mean ± SD		4.0 ± 3.4
Median (IQR)		3.1 (1.8–5.1)
Cognitive characteristics		
Episodic Memory (Z-score)	1,948	
Mean ± SD		0.1 ± 0.9
Median (IQR)		0.0 (–0.6 to 0.7)
Executive Function (Z-score)	1,950	
Mean ± SD		0.1 ± 0.9
Median (IQR)		0.2 (–0.5 to 0.8)
BTACT Composite (Z-score)	1,862	
Mean ± SD		0.1 ± 1.0
Median (IQR)		0.1 (–0.5 to 0.8)

Continuous variables are displayed as mean ± SD, while categorical variables are displayed as *n* (%).

DISCUSSION

To our knowledge, this is the largest study to examine the relationship between beat-to-beat LF-BPV and cognitive function in a diverse community sample. Multivariable regression models controlling for multiple covariates revealed positive associations between both resting systolic and diastolic LF-BPV and executive function and the BTACT composite but not episodic memory. These positive relationships contrasts with numerous studies showing negative relationships between other measures of BPV, i.e., VVV-BP and 24-h ABPV, and cognitive performance[13,14] and with the findings of the one other community study of beat-to-beat BPV and cognitive function, which reported no relationship between LF-BPV and the MoCA.[8] However, comparison of these findings is difficult because of significant differences between studies. First, the MoCA was administered in English, Malay, Chinese, or Tamil, and evidence suggests substantial regional differences in cutoffs for different levels of cognitive function.[15] Second, MoCA scores were positively related to high frequency HF-SBPV and negatively related to the LF:HF BPV ratio. HF-BPV has limited physiological significance because it is driven primarily by changes in intrathoracic pressure associated with respiration and the meaning of the LF:HF BPV ratio is unclear.

The contrasting direction of these relationships underscores the importance of the different BPV time scales as they relate to outcomes.[16] Although somewhat speculative, the negative associations between cognitive indices and VVV-BP and ABPV may relate to silent and functional white matter hyperintensities.[17,18] Global cognitive decline is related to the presence of white matter lesions and degree of leukoaraiosis[19,20] which in turn are related to arterial stiffness and pulsatility.[21,22] In the Baltimore Longitudinal Study of Aging, increased arterial stiffness was associated with cognitive decline.[23] Arterial stiffness was positively associated with SD of 24-h ABP in untreated hypertensive patients[24] and with the coefficient of variation of beat-to-beat SBP in 223 patients within 6 weeks of a transient ischemic attack or minor

Table 2. Unadjusted and adjusted associations between BPV and cognitive function scores in the entire sample ($N = 1,953$)

Cognitive outcome	Blood pressure type	Unadjusted						Adjusting for age (categorical), sex, and education						Adjusting for age (categorical), sex, education, and income					
		n	BPV			BP		*n*	BPV			BP		*n*	BPV			BP	
			b	SE	*P*	*b*	SE	*P*		*b*	SE	*P*	*b*	SE	*P*		*b*	SE	*P*
EMF	Systolic	1,665	0.076	0.029	0.009	−0.004	0.001	<.001	1,662	0.058	0.027	0.033	−0.001	0.001	0.254	848	0.073	0.036	0.04	−0.001	0.002	0.559
	Diastolic	1,665	0.16	0.029	<.001	0.002	0.002	0.348	1,662	0.08	0.029	0.006	0.002	0.002	0.316	848	0.106	0.037	0.004	0.003	0.002	0.189
EFF	Systolic	1,667	0.141	0.028	<.001	−0.001	0.001	0.283	1,664	0.079	0.026	0.002	−0.001	0.001	0.28	850	0.079	0.033	0.018	0	0.001	0.849
	Diastolic	1,667	0.235	0.028	<.001	0.002	0.002	0.297	1,664	0.11	0.027	<.001	−0.002	0.002	0.272	850	0.095	0.035	0.006	0	0.002	0.946
BTACT	Systolic	1,593	0.161	0.03	<.001	−0.002	0.001	0.061	1,590	0.103	0.027	<.001	−0.001	0.001	0.215	823	0.101	0.035	0.004	0	0.001	0.93
	Diastolic	1,593	0.266	0.029	<.001	0.002	0.002	0.245	1,590	0.135	0.028	<.001	−0.001	0.002	0.516	823	0.121	0.037	<.001	0.001	0.002	0.644

Abbreviations: SE, standard error; EMF, episodic memory factor; EFF, executive function factor; BPV, blood pressure variability (mmHg²); BP, blood pressure.

Figure 1. Fitted regression lines with 95% confidence bands for the association of log-transformed systolic and diastolic LF-BPV at rest with z-scores for the BTACT composite index and the episodic memory and executive function factors.

stroke.[25] The negative association between VVV-BP and 24-h ABPV and cognitive function may be the product of increased arterial stiffness but because its association with LF-BPV is unknown, it sheds little light on our finding of a positive relationship between LF-BPV and cognitive function.

In contrast, this positive association is consistent with recent studies suggesting that LF-BPV may have a protective effect, secondary to greater distribution of blood flow, protection of tissue oxygenation, and the clearance of cellular and metabolic debris from interstitial fluid. Higher cerebral blood flow (CBF) was significantly related to better performance in multiple cognitive domains in 2,498 participants in the AGES-Reykjavik Study.[26] Conversely, lower baseline perfusion was associated with more rapid cognitive decline.[27,28] CBF in AD-related brain regions was negatively associated with amyloid-ß load.[29]

In turn, LF-BPV appears to be related to perfusion. Participants more tolerant to central hypovolemia produced by lower body negative pressure and the resultant reduced tissue perfusion had higher levels of LF-BPV compared with those less tolerant.[30] Mathematical modeling studies suggest that these BP oscillations create a pump-like effect in the microvasculature extending perfusion of oxygenated blood further into tissues.[31,32] Inducing 0.1 Hz BP oscillations increases tolerance to hypovolemic challenge,[33] protects cerebral tissue oxygenation,[34] and attenuates the reduction of forearm tissue oxygenation during forearm ischemia.[35] Increases in LF-BPV produced by paced breathing at 0.10 Hz increased tolerance time to presyncope after head-up tilt.[33]

Table 3. Unadjusted and adjusted associations between BPV and cognitive function scores in the sample that had physiological and cognitive assessments within 18 months of one another ($n = 885$)

Cognitive outcome	Blood pressure type	Unadjusted							Adjusting for age (categorical), sex, and education							Adjusting for age (categorical), sex, education, and income						
			BPV			BP				BPV			BP				BPV			BP		
		n	b	SE	P	b	SE	P	n	b	SE	P	b	SE	P	n	b	SE	P	b	SE	P
EMF	Systolic	759	0.015	0.045	0.74	−0.005	0.002	0.01	757	0.018	0.041	0.656	−0.002	0.002	0.252	360	0.013	0.056	0.814	−0.002	0.002	0.487
	Diastolic	759	0.1	0.045	0.026	0.002	0.003	0.589	757	0.043	0.044	0.325	0	0.003	0.977	360	0.048	0.058	0.411	0.001	0.004	0.767
EFF	Systolic	757	0.105	0.042	0.014	−0.002	0.002	0.327	755	0.064	0.038	0.098	−0.001	0.002	0.479	360	0.127	0.049	0.01	0.002	0.002	0.396
	Diastolic	757	0.186	0.042	< 0.001	0.002	0.003	0.486	755	0.085	0.041	0.038	−0.002	0.003	0.449	360	0.131	0.051	0.011	0.001	0.004	0.883
BTACT	Systolic	722	0.114	0.044	0.01	−0.003	0.002	0.193	720	0.081	0.039	0.04	−0.001	0.002	0.592	350	0.129	0.052	0.013	0.001	0.002	0.568
	Diastolic	722	0.214	0.044	< 0.001	0.003	0.003	0.327	720	0.111	0.042	0.008	−0.001	0.003	0.706	350	0.144	0.053	0.007	0.002	0.004	0.653

Abbreviations: SE, standard error; EMF, episodic memory factor; EFF, executive function factor; BPV, blood pressure variability (mmHg²); BP, blood pressure.

Experimental studies also support the impact of LF-BPV on clearance of interstitial fluid. The discovery of a lymphatic system in the brain[36] has advanced our understanding of fluid transport and solute clearance within the cerebral microvasculature and tissues[37] and clearance of cerebral Aß is central to the pathophysiology of AD/ADRD.[38] 0.10 Hz vasomotion is "a potential driving force of metabolic clearance in the brain" (p. 2[39]). Both the glymphatic and intramural periarterial drainage systems involve cerebral LF BP oscillations[40] that facilitate pumping fluid out of interstitial space[37] and down the periarterial drainage pathway.[41,42] Induced 0.02–0.12 Hz vasomotion increased clearance of interstitial fluid in rabbit[43] and mouse models.[42] Importantly, low-frequency BP oscillations have been detected in the brain as well as in the periphery[39] and peripheral and central LF BP oscillations are significantly correlated.[44,45] These studies are consistent with an underlying physiology of a positive association between LF-BPV measured in the periphery and cognitive function.

Even when BPV is expressed in the frequency domain, associations with cognitive function may be frequency specific. Studies of "pulsatility" often show negative relationships to cognition. Greater cerebral pulsatility is linked to cognitive decline.[46,47] Among older but not younger adults, regional cerebral pulsatility was significantly related to greater cortical thinning.[48] Greater pulsatility in the cerebral microcirculation may impair metabolism in neurons and microvascular damage and is associated with cognitive decline.[46] However, "pulsatility" is a high frequency (~1.0 Hz) index based on pressures measured at every cardiac cycle and differs significantly from lower frequency (0.04–0.15 Hz) BP oscillations.

While there is no consensus view on the physiology of LF-BPV, considerable evidence from animal studies supports the existence of oscillations in the low frequency range in sympathetic vasomotor tone[49–51] possibly linked to a central sympathetic oscillator.[52] In normotensive rats, chronic sympathectomy[53] and a-blockade[54] substantially decrease LF-BPV. In a small study of healthy humans, 0.1 Hz oscillations in total peripheral resistance were in phase with oscillations in MAP, suggesting that variation in total peripheral resistance produces variations in MAP,[55] a finding supported by a study in chronically instrumented dogs at rest.[56] Computer simulations show that the LF variations decrease with decreasing sympathetic gains.[57] In dogs, LF oscillations in the left iliac vascular bed exist even after mechanical uncoupling from the central circulation.[58,59]

At least for episodic memory for emotional events, there is some support for a role of the sympathetic nervous system. Acquisition or consolidation of emotional memory is thought to operate through a ß-adrenergic mechanism. Van Stegeren *et al.* administered propranolol, a lipid-soluble ß-blocker that freely crosses the blood–brain barrier and thus acts both centrally and peripherally, nadolol, a ß-blocker that acts only peripherally, and placebo just before participants watched either a neutral or emotionally laden slide show. When tested one week later, those who received propranolol demonstrated impaired recall and recognition compared to the other two groups suggesting the importance of central sympathetic activity in memory.[60] Adrenergic activation, defined as the increase in salivary alpha-amylase during the presentation of a series of neutral and emotional images, was associated with better long-term memory for emotional stimuli in healthy young men and women.[61] Other studies also support the involvement of a ß-adrenergic mechanism in both acquisition[62,63] and retrieval[64] of emotional memories in humans. However, other studies of rodents[65] and humans[66–68] demonstrate the opposite effect: propranolol enhanced rather than reduced

measures of cognitive flexibility, at least under conditions of stress. Thus, the role played by the sympathetic nervous system in associations between cognitive function and LF-BPV is unclear and may depend upon the cognitive operations in question.

Positive associations between LF-BPV and cognitive function may be especially meaningful in the context of the search for biomarkers of early risk of AD, a matter of considerable importance because the pathophysiological process of AD/ADRD begins years before clinical diagnosis. This "preclinical" phase provides a critical opportunity for early intervention, but this requires biomarkers that identify individuals at elevated risk. To date, the best-established biomarkers derive from PET imaging and cerebrospinal fluid, making them expensive, inconvenient, and difficult to access. New fluid-based biomarkers—Aβ42, Aβ40, p-tau217, GFAP, and NfL—appear to have considerable promise but are not yet sufficiently well-established.[69] Our data showing positive associations between LF-BPV and cognitive indices suggest the possibility that LF-BPV also may emerge as an early biomarker of neurodegenerative disorders.

How fluid-based biomarkers and LF-BPV compare as early biomarkers is unknown but some indirect evidence exists. In community-dwelling men and women 65–80 years of age, pTau217 was negatively associated to episodic memory ($b = -0.11 \pm 0.04$, $P = 0.003$).[70] In MIDUS, the association between LF-BPV and episodic memory was significant but positive ($b = 0.079 \pm 0.036$, $P = 0.04$). This relationship was slightly weaker in absolute slope than the episodic memory—pTau217 association reported by Sewell *et al*. Zhang *et al*. reported a significant negative relationship between p-tau181 and executive function ($b = -0.073$, $P = 0.004$) in 686 participants (average age = 73.0 years). In MIDUS, the association between LF-BPV and executive function was similar in absolute strength but positive ($b = 0.073 \pm 0.033$, $P = 0.02$). Differences in measurement of cognitive function, statistical analyses used, and study samples make comparison of these findings challenging but the magnitude of the relationships between the putative biomarkers and cognitive indices, although opposite in direction, was roughly comparable, suggesting that LF-BPV may be as valid a risk biomarker as the fluid-based indices and deserves future investigation.

Strengths and limitations

The study has several notable strengths, primarily that it is a large community study of spectrally defined LF-BPV and cognitive function. Second, the BPV data are part of a comprehensive study of midlife development, including a great many biomarkers and data on cognitive function as well as on daily stress, imaging, and established indices of well-being.

However, several limitations also characterize this study. First, there was considerable variation in the interval between the assessment of cognitive function and LF-BPV in MIDUS, ranging from 1 to 60 months. Because cognitive function declines with age, this interval may have moderated its relationship to LF-BPV. However, executive function and episodic memory show considerable temporal stability over 9 years.[71] Second, analyses limited to participants in whom both indices were collected within 18 months of each other were not significantly different from those from the entire sample, suggesting that this widely ranging measurement interval did not bias the findings. Lastly, we found that the interval between the 2 assessments was not a significant moderator of the strength of the association between any cognitive measure and LF-BPV. Therefore, the variation in the interval between assessment of cognitive function and LF-BPV is unlikely to influence the finding of a positive association between these markers.

Another potential limitation relates to beat-to-beat BP measured at the finger, which is different from pressure measured at other sites. While the degree of variability between BP measured peripherally using a Finometer and centrally using intra-aortic techniques has been deemed acceptable,[72] the separate regulatory mechanisms involved in each vascular system introduce potential error in estimating the BPV experienced by the cerebral circulation based on peripheral measurements.[72] However, recent evidence supports a close relationship between central and peripheral LF-BPV.[44,45]

In this article, we report positive associations between cognitive function and LF-BPV, a finding that contrasts to negative relationships with VVV-BP/ABPV. These findings are consistent with a growing body of evidence linking LF BP oscillations with mechanisms associated with cognitive function—the delivery of oxygenated blood to the brain and clearance of interstitial fluid—suggesting the possibility that LF-BPV may be an accessible biomarker of risk of cognitive decline. Future research will require replication of these findings and further characterization of the underlying mechanisms responsible for low-frequency beat-to-beat BPV and how they may relate to cognitive function.

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Conflict of Interest

The authors declared no conflict of interest.

Author Contributions

Conception and design of the work: J.S., R.P.S., and T.G. Acquisition, analysis or interpretation of data for the work: J.S., T.E.S., M.L., M.W., R.M., R.P.S., T.G., T.-H.C., and M.P. Drafting the work/revising it critically for important intellectual content: J.S., R.P.S., T.-H.C., and M.P.

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