



Parasympathetic and sympathetic nervous systems interactively predict change in cognitive functioning in midlife adults

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Abstract

The two branches of the autonomic nervous system (ANS) have been individually linked to changes in cognitive functioning: The parasympathetic nervous system (PNS) has been associated with healthy cognitive aging, whereas excessive sympathetic nervous system (SNS) activity has been linked to heightened cognitive decline. Despite these separate findings and despite the integrative nature of the ANS, little work has examined the two branches simultaneously to better understand their interactive effects on changes in cognitive functioning in midlife adults. We examined cognitive change in two waves of the Midlife in the United States (MIDUS) study cognitive project and indexed PNS and SNS activity from heart rate variability and epinephrine levels, respectively, from the MIDUS biomarker project (minimum $n = 843$, 57.9% female, mean age at first wave = 53.8 years). Our findings indicate that greater PNS responsivity (i.e., greater withdrawal and greater recovery) in response to cognitive challenge is associated with attenuated cognitive decline, but only among individuals with low SNS levels; at higher SNS levels, the effects of the PNS on cognitive decline are attenuated. These results suggest that future research targeting the ANS and cognitive aging should consider both ANS branch's effects simultaneously.

KEYWORDS

cognitive functioning, epinephrine, heart rate variability, midlife, parasympathetic nervous system, sympathetic nervous system

1 | INTRODUCTION

Cognitive function typically declines with advancing age (Hughes, Agrigoroaei, Jeon, Bruzzese, & Lachman, 2018) and, although normative, cognitive decline is a costly consequence of aging (Hurd, Martorell, Delavande, Mullen, & Langa, 2013). Most research on age-related cognitive decline has focused on older populations and the pathology associated with the clinically relevant loss of cognitive functioning (e.g.,

Alzheimer's disease; Salthouse, 2010). But the early stages of the pathogenesis of cognitive decline are an important point at which interventions to prevent further decline in functionality may be most impactful. Understanding early changes in biological systems that may portend later cognitive decline are, therefore, crucial targets for early intervention to prevent later detrimental consequences of cognitive decline.

The autonomic nervous system (ANS) has been implicated directly in healthy cognitive functioning and indirectly

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in several physiological processes that relate to healthy cognitive functioning (Hugdahl, 1996; Thayer, Hansen, Saus-Rose, & Johnsen, 2009). Two foundational theoretical frameworks support this perspective. The neurovisceral integration model posits that an overlapping set of neural structures regulates both the parasympathetic nervous system (PNS) and cognitive functioning (Thayer & Lane, 2000). This neural architecture co-occurs in cortical-subcortical networks connected to the ventromedial prefrontal cortex (vmPFC), an area of the brain that demonstrates robust associations with so-called “top-down” control of cognition and executive function (Alvarez & Emory, 2006; Thayer, Ash, Fredrikson, Sollers, & Wager, 2012). In a second, complementary framework, polyvagal theory (Porges, 1995), higher level brain structures are postulated to be intricately linked to ANS activity (and PNS activity specifically) in order to modulate energy usage in pursuit of avoiding threat and facilitating social functions. Further, polyvagal theory describes the PNS's inhibitory relationship with the sympathetic nervous system (SNS) and other metabolic systems. Rapid inhibition and disinhibition of this “vagal brake” in response to challenge results in efficient mobilization of energy and an effective return to calm states, respectively (Porges, 2007). These theoretical frameworks thus suggest PNS activity may relate to or directly support cognitive functioning via neural and metabolic pathways.

Accordingly, increased indices of PNS activity, such as higher levels of high-frequency heart rate variability (HF HRV)—a measure of cardiac PNS functioning—has been associated with better performance on several measures of executive function (Thayer et al., 2009). HF HRV is also thought to be a trait-like predictor of individual differences in cognitive control, implicated in a variety of psychopathologies marked by deficits in self-regulation (Beauchaine & Thayer, 2015). Indeed, meta-analyses estimate a significant, small association of higher PNS activity with better “top-down” regulation of cognitive functioning and other behavioral and emotional processes, with some evidence that publication bias may inflate these associations (Holzman & Bridgett, 2017; Zahn et al., 2016). This pattern has been observed cross-sectionally and prospectively in mid-life adults (Frewen et al., 2013; Zeki Al Hazzouri, Elfassy, Carnethon, Lloyd-Jones, & Yaffe, 2017). However, other research failed to find strong support for integrated neural control of both parasympathetic activity and cognitive functioning in the forebrain despite observing correlations between HF HRV and two cognitive tests (a test of working memory and interference control; Jennings, Allen, Gianaros, Thayer, & Manuck, 2015).

Within longitudinal studies, the association of PNS activity and change in cognitive functioning is somewhat inconsistent as well: Higher resting PNS activity has been linked to attenuated declines in some aspects of cognitive functioning in older adults (Mahinrad et al., 2016); other work has not found associations between PNS activity and changes in cognitive functioning in mid-life adults (Britton et al., 2008).

The degree to which the PNS reacts to and recovers from a cognitive task has been related to cognitive functioning as well. Within polyvagal theory, a robust PNS withdrawal and subsequent recovery indicates a well-regulated mobilization of energy to meet the needs of a given challenge (Porges, 2001, 2007), such as a cognitive task. Faster recovery of PNS activity after a cognitive challenge has been associated with improved task-switching performance, a measure of executive functioning (Kimhy et al., 2013). In other work, greater PNS responsivity to cognitive challenge—that is, a strong, parasympathetic withdrawal and/or a strong recovery, which has also been labeled “parasympathetic flexibility” (Miller et al., 2013)—has been linked to improved performance on broad tests of cognitive functioning (e.g., Stroop: Mathewson, et al., 2010; anchoring and adjusting: Kassam et al., 2009; attentional capacity: Duschek, Muckenthaler, Werner, & del Paso, 2009).

Overall, indices of resting PNS activity and PNS responsivity have been associated with cognitive functioning, with mixed evidence suggestive that PNS activity may relate to longer term changes in cognitive functioning. However, the PNS is only one half of the ANS and works in tandem with the SNS to regulate physiological arousal and allostasis (Karatsoreos & McEwen, 2011). The SNS is responsible for activation of the classic “fight or flight” response to stressors and, within the neurovisceral integration and polyvagal frameworks, is posited to be under the inhibitory control of the prefrontal cortex (Porges, 2007; Thayer & Lane, 2000, 2009). Thus, although the two branches do function independently, they work in concert to maintain proper physiological activation for an organism's present needs (Porges, 2001). This interdependence between the two branches of the ANS may be best conceptualized as autonomic space (Berntson, Cacioppo, & Quigley, 1993). Because of the potent effects of sympathetic activation on physiological arousal, inhibition of the SNS at rest is thought to allow the PNS to regulate energy expenditure on a moment-to-moment basis that results in better-regulated physiological activations to meet nonthreatening demands (Thayer & Lane, 2009).

Like the PNS, the SNS has been independently linked to cognitive functioning (Giuliano et al., 2018). Moderate levels of resting SNS activation may support physiological arousal necessary for cognitive functioning (Lovallo, 2011; Yerkes & Dodson, 1908). Other work has found that impaired sympathetic activity is associated with dementia among individuals with Parkinson's Disease (Poewe, 2007) and that pharmacologically blocking sympathetic activity impairs episodic memory for emotional stimuli (van Stegeren, Everaerd, Cahill, McGaugh, & Gooren, 1998). But over longer term periods, chronic activation of the SNS can lead to a cascade of negative, downstream consequences on the neural and vascular anatomy that supports

healthy cognitive aging (McEwen, 1998; Rozanski & Kubzansky, 2005). This work suggests that moderate levels of SNS activity may play a role in maintaining healthy cognitive functioning but may also lead to decrements in cognitive functioning at higher levels of activity.

Few studies have examined the PNS and SNS as interactive influences on cognitive functioning, despite burgeoning evidence of the ANS' influence on cognitive functioning and the known interdependence of its two branches. In one study, phasic PNS fluctuations were associated with better working memory performance but resting SNS activity moderated this association in a sample of young mothers considered at-risk for chronic stress (Giuliano, Gatzke-Kopp, Roos, & Skowron, 2017). Elevated PNS activity was associated with greater working memory capacity, but only when resting SNS activity was low; higher levels of resting SNS activity blocked the association between PNS fluctuations and working memory capacity. However, the interactive relationship of the PNS and SNS on long-term changes in cognitive function across the lifespan is unknown.

We examined the contribution of both branches of the ANS to changes in cognitive function across two waves of the MIDUS study (approximately nine years' time). Based on prior evidence in younger samples (Giuliano et al., 2017), we hypothesized that the interaction of the PNS and SNS would be significantly related to changes in cognitive functioning, such that higher PNS responsivity would relate to attenuated decline in cognitive functioning when SNS activity was lower but not when SNS activity was higher.

2 | METHOD

The Midlife in the United States (MIDUS) is a national longitudinal study of health and well-being that allows researchers to evaluate aging as an integrated bio-psycho-social process (Ryff & Kruger, 2019). Current data span thirty years in three collection waves, each wave separated by approximately ten years. Biomarker data from the second wave (MIDUS 2) and cognitive data from both the second and third wave (MIDUS 3) are used in the current analysis.

2.1 | Biomarker subproject

The biomarker subproject of MIDUS 2 was conducted 2004–2006 on a sample of 1,255 respondents, all of whom completed an initial baseline survey. Comprehensive biological assessments were performed on this sample subset at three general clinical research centers (UCLA, University of Wisconsin, and Georgetown University).

2.1.1 | Sympathetic nervous system

As part of a broader examination of biopsychosocial health, 12-hr urinary samples were collected. SNS tone was primarily evaluated using 12-hr urine epinephrine (EPI) concentration, adjusted for creatinine levels.¹ EPI concentrations were submitted to natural-log transformation to correct a positive skew in the distribution. We followed-up our analyses on EPI with exploratory analyses that replicated our primary models but with EPI replaced by creatinine-corrected norepinephrine concentrations, another marker of SNS tone (Grassli & Esler, 1999).

2.1.2 | Parasympathetic nervous system

PNS control of heart rate is achieved through efferent traffic of the vagus nerve to the sinoatrial node. Vagus nerve traffic, or vagal tone, responds rapidly to stimuli and regulates beat-to-beat fluctuations in heart rate. Thus, in order to examine PNS activity, relative power of the high frequency component of heart rate variability (HF HRV) was derived from ECG recordings. Inter-beat intervals from the HR series from each five-minute epoch were interpolated into the frequency domain. The high-frequency component (0.15–0.4 Hz) of the waveform is thought to emanate solely from PNS control (Berntson et al., 1997). HF HRV values were natural-log transformed to correct a positive skew in the distribution.

Baseline PNS and dynamic PNS responses

To index baseline PNS functioning, participants were seated for ten minutes while ECG was recorded continuously. Dynamic PNS responses were indexed from HRV recorded during two cognitive tasks presented during the Biomarker subproject. These tasks consisted of a math task and the Stroop color-naming task that were adaptively adjusted to maintain similar levels of difficulty for each participant.² Task order was randomized across participants. HR was recorded continuously during these tasks and during five-minute recovery periods that followed each task.

In line with prior work based on the MIDUS study sample (Crowley et al., 2016; Kimhy et al., 2013), we focused on PNS recovery scores, which were produced by subtracting the task HF HRV from the HF HRV of the epoch immediately following each task (i.e., the first recovery period for the first

¹Low-frequency heart rate variability (LF HRV) is available in the MIDUS project data as well and had been theorized to link to sympathetic activity. However, more recent work suggests LF HRV is not a reliable indicator of cardiovascular sympathetic activity (Heathers, 2011).

²Because of the adaptive nature of these tasks, performance outcomes are not suitable indices of cognitive functioning.

task and the second recovery period for the second task) and averaging the two differences. Larger negative values indicate an attenuated PNS recovery; larger positive values indicate heightened PNS recovery. Simple subtractive change scores across epochs are appropriate for indexing general responses across multiple tasks (Llabre, Spitzer, Saab, Ironson, & Schneiderman, 1991).

We also examined reactivity scores, which we produced by subtracting the HF HRV value from the epoch immediately preceding each task (i.e., the baseline epoch for the first task and the recovery period that preceded the second task) from the task HF HRV and averaged the two differences. For this measure of reactivity, larger negative values indicate heightened PNS withdrawal (reactivity) in response to the cognitive tasks; larger positive values indicate reduced PNS withdrawal (reactivity) in response to the cognitive tasks.

Quadratic index of PNS responsivity

As a follow-up to the individual PNS recovery and reactivity indices, we explored an integrative measure of PNS responsivity indexed by the quadratic pattern of the HF HRV response to cognitive challenge. For each of the cognitive challenges (i.e., math and Stroop tasks), a quadratic line was fit for each participant to the HF HRV value from the epoch that preceded the task, the task epoch, and the epoch that followed the task; the model also included a fixed effect for the linear line through these three epochs. The resulting quadratic estimates were normalized (z score) across the sample within each cognitive task. These normalized values were averaged into a single index of PNS responsivity—that is, the degree to which the PNS reacted to and recovered from the cognitive challenges (Miller et al., 2013). With this index, larger positive numbers are indicative of greater PNS responsivity.

2.1.3 | Orthostatic (physical) challenge

Orthostasis, or changing positions from sitting to standing, results in venous blood pooling as circulating blood volume shifts from the chest to the distensible venous capacitance system below the diaphragm (Abhoud et al., 1976; Nordkamp, van Dijk, & Wieling, 2013). To compensate for the resulting drop in blood pressure, a series of cardiopulmonary reflexes ultimately result in reduced parasympathetic activity and increased sympathetic activity. Hence, measuring reactivity to orthostasis provides an index of autonomic response to a purely physical challenge. Such cardiovascular reflexes may be less likely to be associated with central nervous system activity relevant to cognitive functioning (Porges, 2007). Comparing PNS responsivity in orthostatic and cognitive

challenges allows for examination of the specificity of the interactive autonomic associations with change in cognitive functioning.

Participants were exposed to the orthostatic challenge following the cognitive tasks. Participants stood and, after a several minute calibration period, cardiovascular data were recorded for 5 min. We calculated an index of PNS reactivity to this orthostatic challenge by subtracting HF HRV in the last recovery epoch of the cognitive challenges from the HF HRV while standing (i.e., larger negative values indicate greater PNS withdrawal in response to physical challenge). There was no recovery period following orthostatic challenge.

2.2 | Cognitive subproject

The MIDUS 2 cognitive subproject was conducted 2004–2006 on a sample of 3,487 respondents, all of whom completed the initial baseline survey. The subsequent MIDUS 3 cognitive project was conducted approximately 10 years later on a sample of 2,693 respondents. The goal of the cognitive project was to determine how cognition is related overall to mental and physical health. During each wave of assessment, the Brief Test of Adult Cognition by Telephone (BTACT; Kimhy et al., 2013; Tun & Lachman, 2006) was administered to the participants. The BTACT includes subtests that measure episodic memory (immediate recall and delayed recall of a 15-word list), working memory span (backward digit span), verbal fluency (category fluency), inductive reasoning (number series completion), speed of processing (backward counting task), and reaction time (task-switching test).

Prior research on the MIDUS sample showed that: (a) both word recall tests loaded onto an episodic memory factor and the rest of the subtests loaded onto an executive function factor (i.e., factor eigen values >1 in exploratory factor analysis); (b) the BTACT had good concurrent and discriminant validity; and (c) significant differences due to mode of testing (in-person or telephone) were not evident among a subset of participants (Lachman, Agrigoroaei, Tun, & Weaver, 2014). In other work, the BTACT has been shown to have good test-retest reliability across two (reliability coefficients range from $r = .55$ to $.94$) and four weeks ($r = .52$ to $.85$, except for category fluency, $r = .28$; Lachman et al., 2014; Whitbourne, Neupert, & Lachman, 2008). In the MIDUS 3 cognitive project, the same episodic and executive functioning factors were evident and were equivalent across occasions (i.e., tests of longitudinal measurement invariance fit a weak invariance model; Hughes et al., 2018). Our analyses focus on the summary BTACT score at each time point; see supplement for analyses of the individual episodic memory and executive functioning factors.

2.3 | Analyses

2.3.1 | Primary

To examine the interactive effects of PNS and SNS on changes in cognitive functioning, multilevel models were specified that regressed cognitive functioning (i.e., BTACT score) on a three-way, cross-level interaction between a dummy code representing the MIDUS wave (MIDUS Wave 2 = 0; MIDUS Wave 3 = 1), HF HRV (baseline, recovery, or reactivity), and EPI concentration.

2.3.2 | Secondary

We followed the primary analyses with several secondary analyses: (a) We substituted the quadratic index of PNS responsiveness for the individual measures of PNS recovery or reactivity; (b) we explored if age moderated the relationship between change in cognitive functioning and the interactive effects of PNS and SNS; (c) we repeated the primary models with creatinine-corrected norepinephrine levels (NE) replacing EPI levels as an indicator of SNS activity; (d) we re-ran the models using PNS reactivity to orthostatic challenge as the index of parasympathetic activity, which allows for the examination of the specificity of the PNS

response to cognitive challenge compared to physical challenge; (e) due to collinearity between heart rate and HRV (de Geus, Gianaros, Brindle, Jennings, & Berntson, 2019), we re-ran models with baseline heart rate and heart rate reactivity and recovery replacing the HF HRV measures; (f) finally, we examined gender as a moderator due to known gender differences in cognitive decline in older adults (Lin et al., 2015).

2.3.3 | Covariates

All analyses co-varied participant gender (Male = 0; Female = 1), age at MIDUS 2 (centered at age = 50), and the number of years between completing the MIDUS 2 and MIDUS 3 cognitive sub-studies. As in prior work (Crowley et al., 2011, 2016), prescription and over-the-counter medications that could alter cardiovascular, autonomic, or cognitive functioning were counted for each participant and included as a continuous covariate (Table 1). Participants' self-reported whether they had experienced any of a series of health conditions (Table 2); their answers of the following conditions were included as dummy-coded covariates in each model ("Yes" or "Borderline" = 1; "No" or "Unsure" = 0): Heart disease, high blood pressure, circulation problems, heart murmur, stroke, emphysema, and depression.

TABLE 1 Usage frequencies of drug classes that may affect autonomic, cardiovascular, or cognitive functioning

Drug Class	AHFS Pharmacologic-Therapeutic classification #	Participants reporting usage (number of reported uses)	Percent of sample reporting usage
Parasympathomimetic (Cholinergic) Agents	120400	2	0.23
Sympathomimetic (Adrenergic) Agents	121200	44 (52)	5.06
Sympatholytic (Adrenergic Blocking) Agents	121600	4	0.46
Autonomic Drugs, Miscellaneous	129200	2	0.23
a-Adrenergic Blocking Agents	242000	14	1.61
b-Adrenergic Blocking Agents	242400	113	13.00
Dihydropyridines	242808	39	4.49
Calcium-Channel Blocking Agents, Miscellaneous	242892	18	2.07
Angiotensin-Converting Enzyme Inhibitors	243204	92	10.59
Angiotensin II Receptor Antagonists	243208	60	6.90
Selective Serotonin Agonists	283228	13	1.50
Adrenals	680400	39 (41)	4.49
Selective Serotonin- and Norepinephrine-reuptake Inhibitors	28160416	21	2.42
Selective-serotonin Reuptake Inhibitors	28160420	77	8.86
Serotonin Modulators	28160424	9	1.04
Tricyclics and Other Norepinephrine-reuptake Inhibitors	28160428	16	1.84
Antidepressants, Miscellaneous	28160492	11	1.27

Condition	Participants reporting conditions	Percent of sample reporting condition
Heart Disease	72	8.29
High Blood Pressure	291	33.49
Circulation problems	77	8.86
Heart Murmur	110	12.66
TIA or Stroke	27	3.11
Emphysema/COPD	22	2.53
Depression	199	22.90

TABLE 2 Frequencies of health conditions that may impact HF HRV or cognitive functioning

Thus, the model to test Time \times HF HRV \times EPI for participant j at MIDUS wave i consisted of:

Level 1:

$$\text{Cognition}_{ij} = \beta_0 + \beta_1 \text{Wave}_{ij} + \mu_{ij}$$

Level 2:

$$\begin{aligned} \beta_0 = & \gamma_{00} + \gamma_{01} \text{HRV}_j + \gamma_{02} \text{EPI}_j + \gamma_{03} \text{HRV} * \text{EPI}_j \\ & + \gamma_{04} \text{Gender}_j + \gamma_{05} \text{Age}_j + \gamma_{06} \text{WaveTime}_j \\ & + \gamma_{07} \text{Medications}_j + \gamma_{0y} \text{MedicalCondition}_j + \varepsilon_j \end{aligned}$$

$$\beta_1 = \gamma_{10} + \gamma_{11} \text{HRV}_j + \gamma_{12} \text{EPI}_j + \gamma_{13} \text{HRV} * \text{EPI}_j$$

where $\gamma_{0y} \text{MedicalCondition}_j$ represents the list of dummy-coded medical conditions for participant j . Secondary analyses added age as an additional cross-level moderator or replaced EPI concentration with creatinine-corrected NE concentration. A random intercept for Wave_{ij} per participants was included in every model.

All analyses were run in R (v3.5.1; R core team, 2018) using the lme4 package (Bates, Maechler, Bolker, & Walker, 2015). Graphs were produced using the ggplot2 package (Wickham, 2009). All code is available on OSF (<https://osf.io/yt49f/>), and data for the MIDUS studies can be accessed via the Inter-university Consortium for Political and Social Research (<https://www.icpsr.umich.edu/icpsrweb/ICPSR/series/203>).

3 | RESULTS

3.1 | Participants

Participants ($n = 944$; 57.9% female; mean age at MIDUS 2 = 54.2 years, $SD = 10.9$, range = [34, 83]) included in the current analysis completed MIDUS 2 and MIDUS 3 on average nine years apart (Mean = 9.34 years, $SD = 0.83$, range = [8, 12]). Of the 944 participants, $n = 14$ were missing urine epinephrine data, and $n = 2$ were missing both waves'

BTACT cognition scores and so were excluded from those analyses. An additional $n = 73$ were missing 1 BTACT score, but these participants were included in analyses as multilevel models can generally account for this degree of missingness. Participants who were missing baseline HF HRV ($n = 63$), HF HRV reactivity ($n = 77$), or HF HRV recovery ($n = 88$) data were excluded from those specific analyses. Our final sample size thus varied depending on the analysis being conducted (baseline HRV: $n = 867$; HRV reactivity: $n = 854$; HRV recovery: $n = 843$). In the largest of these analytic samples, 81% identified as European-American, 14% as African-American, 3% as multiracial, and 2% were of some other racial identity; 4% of the sample identified as Hispanic.

3.2 | Preliminary results

As reported elsewhere (Hughes et al., 2018), cognitive functioning as measured by the summary BTACT score generally declined in this subsample across the approximately 10 years from MIDUS 2 to MIDUS 3 ($B = -0.184$, 95% CI [-0.223, -0.145], $p < .001$); similar patterns are evident for episodic memory ($B = -0.117$, [-0.179, -0.056], $p < .001$) and executive functioning score ($B = -0.326$, [-0.363, -0.289], $p < .001$). See Table 3 for descriptive statistics of study variables.

3.3 | Autonomic predictors of changes in cognitive functioning

3.3.1 | Baseline ANS functioning

Baseline PNS activity was linked to marginal changes in BTACT scores from MIDUS 2 to MIDUS 3 (Wave \times HF HRV: $B = 0.030$, [-0.001, 0.061], $p = .057$), which seems to be driven by executive functioning (Wave \times HF HRV: $B = 0.035$, [0.005, 0.061], $p = .020$; Table S1). These analyses suggest that higher vagal tone (i.e., greater HF HRV values) at rest related to attenuated declines in cognitive functioning. In contrast, baseline SNS activity was not associated with

TABLE 3 Means (*SD* or range) of study variables^a

	Full Sample (<i>n</i> = 869) ^a
Age (years)	
MIDUS 2, biomarker project	53.8 (10.9)
MIDUS 3, cognitive project	63.1 (10.9)
BTACT scores (standardized units)	
MIDUS 2	0.194 (0.928)
MIDUS 3	0.032 (0.667)
Parasympathetic nervous system (high-frequency heart rate variability, natural-log ms ²)	
Baseline	4.91 (1.26)
Stroop	4.32 (1.29)
Stroop recovery	4.90 (1.27)
Math	4.74 (1.23)
Math recovery	4.91 (1.25)
Orthostatic challenge	4.08 (1.32)
Mean cognitive reactivity	-0.357 (0.579)
Mean cognitive recovery	0.357 (0.624)
Orthostatic challenge reactivity	-0.856 (0.879)
Sympathetic nervous system (creatinine-corrected, µg/g)	
Epinephrine	0.144 (0.118)
Norepinephrine	2.03 (1.59)

^aFull sample in this table includes participants with epinephrine data available, at least one BTACT score, and HF HRV baseline, reactivity, or recovery data available.

change in cognitive functioning scores (Wave × EPI: $p_s \geq .1$; Table S2).

3.3.2 | PNS responsivity to cognitive challenge

PNS recovery from the cognitive tasks in the Biomarker project predicted change in BTACT scores ($B = 0.071$, [0.007, 0.135], $p = .030$; Table S3). Here again, higher vagal tone (as indexed by greater HF HRV recovery from the laboratory tasks) was associated with weaker declines in cognitive functioning. PNS reactivity to the cognitive tasks was not associated with changes in cognitive functioning (Wave × HF HRV: $p_s > .15$).

3.4 | Interactive effects of PNS and SNS on change in cognitive functioning

3.4.1 | Baseline PNS measure

Baseline PNS and SNS activity were not found to interactively predict change in cognitive functioning ($p_s > .12$).

3.4.2 | PNS responsivity to cognitive challenge

PNS recovery

SNS activity was found to moderate the association of dynamic PNS response with changes in cognitive functioning. Specifically, Wave × PNS recovery × SNS was associated with changes in BTACT scores ($B = -0.176$, [-0.305, -0.048], $p = .007$). This association was reflected in executive functioning scores ($B = -0.248$, [-0.367, -0.130], $p < .001$) more so than episodic memory scores (Table S4). We explored this interaction by plotting point estimates of the slope linking MIDUS 2 to MIDUS 3 BTACT scores across the range of PNS recovery scores for individuals with low ($-1 SD$) and high ($+1 SD$) epinephrine concentrations. We subsequently calculated simple slopes for the change in BTACT scores from MIDUS 2 to MIDUS 3 at high and low PNS recovery and epinephrine levels. For individuals with lower SNS activity, PNS recovery was positively associated with changes in BTACT scores—that is, stronger HF HRV recovery from the laboratory tasks predicted attenuated declines in cognitive functioning (estimate of MIDUS 2 to MIDUS 3 simple slope at $+1 SD$ HRV recovery: $B = -0.104$, [-0.188, -0.019]) and weaker HF HRV recovery predicted greater declines in cognitive functioning ($-1 SD$ HRV recovery: $B = -0.321$, [-0.402, -0.240]; Figure 1). But at higher levels of SNS activity, BTACT changes were roughly equivalent at high ($B = -0.168$, [-0.248, -0.087]) and low PNS recovery scores ($B = -0.137$, [-0.218, -0.056]), suggesting the association between PNS recovery and BTACT changes was blocked.

PNS reactivity

An interaction between PNS reactivity and SNS levels on changes in BTACT score was also found (Wave × PNS reactivity × SNS: $B = 0.192$, [0.054, 0.330], $p = .006$), which was reflected in both executive functioning and episodic memory (Table S5). However, decomposing this interaction in a manner similar to the PNS recovery analysis revealed that the association of PNS reactivity with changes in BTACT score was seemingly in the opposite direction of the effect observed for PNS recovery. For individuals with low SNS activity, PNS reactivity correlated *negatively* with change in BTACT scores; greater PNS withdrawal (larger, negative PNS reactivity values) in response to the cognitive challenge predicted attenuated declines in cognitive functioning ($-1 SD$ PNS reactivity: $B = -0.121$, [-0.203, -0.039]) and weaker PNS withdrawal was associated with greater declines ($+1 SD$ PNS reactivity: $B = -0.305$, [-0.385, -0.225]; Figure 1). But at higher SNS activity levels, BTACT changes were roughly equivalent for individuals with greater ($B = -0.189$, [-0.271, -0.108]) and weaker PNS withdrawal ($B = -0.123$, [-0.204, -0.043]).

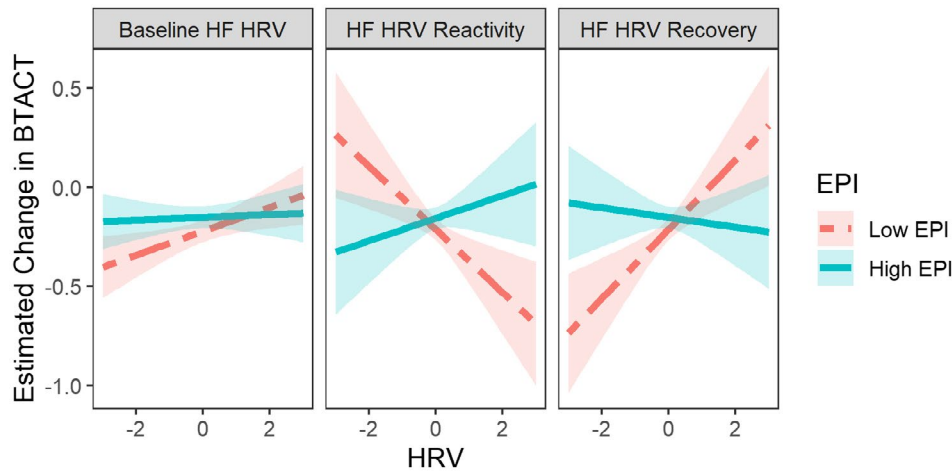


FIGURE 1 Estimated change in BTACT scores (MIDUS 3 – MIDUS 2) at ± 1 SD EPI concentration across a range of HF HRV values. Point estimates of change in BTACT represent the slope connecting MIDUS 2 to MIDUS 3 derived from the multilevel model. Larger positive HRV values for baseline and recovery represent stronger vagal tone; larger negative HRV values for reactivity represent greater PNS vagal withdrawal

3.5 | Secondary analyses

3.5.1 | Quadratic index of parasympathetic responsivity

Integrating across the results for the two indices of dynamic PNS activity suggests that PNS responsivity—greater withdrawal, greater recovery—is associated with improved cognitive functioning under conditions of low SNS activity, and that high SNS activity blocks this association. Here, we examined PNS responsivity more formally by replacing reactivity or recovery with a quadratic index that encapsulates the reactivity and recovery measures. Unsurprisingly, this model revealed a similar pattern of results when PNS responsivity was more formally tested (Wave \times PNS responsivity \times SNS: $B = -0.128$, $[-0.218, -0.037]$, $p = .006$; Table S6). For individuals with lower SNS activity, PNS responsivity was positively associated with changes in BTACT scores—that is, greater responsivity predicted attenuated declines in cognitive functioning ($B = -0.111$, $[-0.194, 0.028]$) and weaker responsivity predicted stronger declines ($B = -0.316$, $[-0.396, -0.236]$)—but at higher levels of SNS activity, BTACT changes across MIDUS waves were roughly equivalent at high ($B = -0.177$, $[-0.258, -0.096]$) and low PNS responsivity scores ($B = -0.129$, $[-0.209, -0.048]$).

3.5.2 | Interactions with age

We examined if the patterns observed were evident across the age range in the MIDUS study. Age did not robustly moderate the Wave \times PNS recovery \times SNS interaction on changes in BTACT scores ($B = 0.011$, $[0.001, 0.023]$, $p = .062$); weaker

effects were evident for baseline PNS ($B = 0.004$, $[0.001, 0.009]$, $p = .102$) and PNS reactivity ($B = -0.011$, $[-0.023, 0.002]$, $p = .104$; Table S7), though the direction of the effect was similar across all indices (see Figure S1). These exploratory results are, therefore, inconclusive due to their relative weakness and lack of consistency across PNS measures.

3.5.3 | Other indices of SNS activity

We repeated our analyses with creatinine-corrected nor-epinephrine (NE) concentrations replacing epinephrine. Models with NE generally replicate the effects seen with EPI. Specifically, NE moderates the association of PNS recovery and reactivity with changes in cognitive functioning (Table S8, Figure S2); this interaction was not evident for baseline PNS activity. The interactive effects were in the same direction as the EPI analyses. This suggests that the interaction between PNS and SNS on changes in cognitive functioning is not specific to one index of SNS activity.

3.5.4 | Orthostatic challenge

We examined if the interaction between PNS reactivity to a physical challenge (orthostasis, or standing upright) and SNS activity predicted changes in cognitive functioning. Unlike the PNS responses to cognitive challenge, PNS reactivity to physical challenge did not interactively predict change in cognitive functioning with SNS ($B = 0.030$, $[-0.053, 0.113]$, $p = .483$; Table S9). Thus, the prospective links between SNS activity and changes in cognitive function appear to be specific to dynamic responses to cognitive, and not physical challenges.

3.5.5 | Examining HR instead of PNS activity

We examined if the HR \times SNS interaction similarly predicted change in cognitive functioning. Replacing PNS activity with HR did not replicate the primary models (Baseline HR: $B = 0.0002$, $[-0.007, 0.007]$, $p = .943$; HR reactivity: $B = -0.012$, $[-0.031, 0.007]$, $p = .214$; HR recovery: $B = 0.0135$, $[-0.006, 0.0330]$, $p = .173$). This indicates the effect may be specific to PNS activity as indexed by HF HRV.

3.5.6 | Gender differences

Finally, we explored gender differences in the PNS \times SNS interaction. A main effect of gender was evident such that women demonstrated higher episodic memory and men demonstrated higher executive functioning (all $ps \leq .002$; see Tables S1-S5). Because of the opposing directions of these effects, no gender differences were evident for BTACT scores. Robust differences between men and women were not evident in the association of the PNS \times SNS interaction with change in cognitive functioning ($B = -0.055$, $[-0.321, 0.211]$, $p = .686$).

4 | DISCUSSION

Using a novel integrative model of the two branches of the ANS, our study demonstrates that changes in cognitive functioning are predicted by the interactive effects of the PNS and the SNS in midlife adults. Previous theorizing and literature examining the ANS has focused almost exclusively on linking PNS or SNS activity separately to outcome measurements (Greaney, Kenney, & Alexander, 2017; Thayer & Lane, 2000). Following prior evidence that the PNS and SNS interactively predict working memory in a sample of young, at-risk mothers (Giuliano et al., 2017), here, we show the interactive effect of the ANS extends to predicting broader changes in cognitive functioning across a nine-year period in a sample of middle-aged men and women. The best maintenance of cognitive function was predicted by a combination of stronger PNS responsivity to cognitive challenge (i.e., stronger withdrawal and stronger recovery) and lower SNS activity. These results appeared to be specific to responses to the cognitive challenge; PNS reactivity to orthostatic challenge did not predict changes in cognitive functioning.

The results in this study were most robustly observed when PNS responsivity, or the strength of reactivity and recovery, to a cognitive challenge were considered, rather than baseline PNS functioning. These results are in line with initial evidence of the interactive ANS effects on working memory, which were based on dynamic PNS responses to a

cognitive task moderated by resting SNS activity (Giuliano et al., 2017). Dynamic PNS responses may impact cognitive function more so when SNS activity is low due to a wider range of variability available in autonomic space for the PNS to withdrawal, as opposed to when SNS activity is high and physiological activation is near ceiling, leaving less autonomic space for PNS withdrawal to further increase physiological arousal (Berntson, Caccioppo, & Quigley, 1993a).

The effects observed here—in which autonomic measurement occurred independent of the first wave of cognitive testing and nearly ten years before the second wave—suggest that PNS responsivity to cognitive challenges may be a trait-like indicator of the psychophysiological processes underlying cognitive functioning. These findings are also consistent with longitudinal work in young children showing that individual-level variance in PNS activity during laboratory visits is primarily accounted for by trait-level variance (Gatzke-Kopp & Ram, 2018). The present results extend prior research showing that trait-like measures of PNS and SNS activity make independent contributions to neural mechanisms of executive function (Giuliano et al., 2018).

The prospective effects on cognitive functioning observed here may also be explained by peripheral interactions between the ANS branches. In some prior work, greater PNS responsivity was associated with reduced carotid atherosclerosis in young to early-midlife adults (Heponiemi et al., 2007). The SNS is classically viewed as one part of the redundant systems that regulate vascular contractility (de Lucia, Piedepalumbo, Paolisso, & Koch, 2019). These peripheral physiological outcomes may each impact blood flow to the brain, which could subsequently impact cognitive functioning. Further, increasing the vasodilation capabilities of small arterioles and capillaries—for example, via aerobic exercise and concomitant increases in PNS activity and reductions in SNS activity (Hyodo et al., 2012; Mueller, 2007)—can increase the nutrient delivery to the brain and consequently increasing cognitive function (Ogoh, Hayashi, Inagaki, Ainslie, & Miyamoto, 2008).

Other work suggests PNS responsivity to a cognitive task may indicate a trait-like ability to orient to and cope with challenging tasks (Porges, 2001; Thayer et al., 2012) or to adaptively expend energy in the face of challenge (Duschek et al., 2009); each process may in turn optimize cognitive functioning. A comparison to PNS responsivity to orthostatic challenge—a purely physical task—further indicates the specificity of the results to cognitive challenge; however, the orthostatic challenge did not contain a recovery period, somewhat limiting this comparison. The present findings suggest these PNS responses are more beneficial when SNS activity is low; higher SNS activity, perhaps indexing higher chronic stress levels (Cacioppo et al., 2000; Lucini et al., 2005; Pike et al., 1997), may blunt these salubrious peripheral mechanisms.

4.1 | Limitations

Guiding theoretical frameworks, the neurovisceral integration (Thayer & Lane, 2000) and polyvagal models (Porges, 1995), suggest direct links between PNS activity as indexed by HF HRV and central nervous system functioning that may underlie cognitive functioning (but *cf.* Jennings et al., 2015). Hence, longitudinal changes in autonomic functioning may co-occur with changes in cognitive functioning. In this analysis, we examined longitudinal changes in cognitive function, but biomarker data were only available from one time point (MIDUS 2). It is not clear if the associations observed with change in cognitive functioning would be evident at individual time points; indeed, interactive effects were not robust at the baseline cognitive measurement when accounting for longitudinal change in cognitive functioning. Future work should examine ANS biomarkers measured simultaneous to cognitive testing to determine if changes in ANS co-occur with changes in cognitive functioning. Future work may also attempt to modulate ANS functioning via behavioral or pharmacological intervention to examine putative mechanistic pathways.

The BTACT provides an effective way to examine broad cognitive health outcomes at scale but is not focal in terms of exact cognitive processes that may be impacted across time. We note in supplementary analyses that the episodic memory and executive functioning factors generally paralleled the primary results focused on the summary BTACT score. Future examinations of autonomic contributions to cognitive health would benefit from more specific tests of cognitive functioning like those found in prior work (e.g., visuospatial working memory; Giuliano et al., 2017).

This report relied on creatinine-corrected urinary epinephrine as an index of baseline measurements of SNS activity. This measure of SNS activity is the result of an array of downstream processes operating over the course of several hours; in comparison, HF HRV is considered fairly specific to the PNS and operates on the order of hundreds of milliseconds (Berntson et al., 1993b; Thayer & Lane, 2000). Such differences in measurement specificity and systemic breadth may impede interpretation or useful translation of these results. Future work could focus on more direct indices of SNS activity, measured using techniques like microneurography (Greaney et al., 2017) or impedance cardiography (Goedhart, Kupper, Willemsen, Boomsma, & de Geus, 2006), which may better match the timescale of the PNS measures and could be indexed concurrent to the cognitive tasks.

Finally, two demographic issues may limit interpretation. First, longitudinal studies consistently retain subjects that are healthier than the average person within the target population. In one examination of changes in cognitive functioning, attrition was modeled as a significant contributor to a sample's decline in cognitive functioning (Sliwinski, Hofer, Hall, Buschke, & Lipton, 2003). This survivor bias also suggests that the present

results may not generalize to more clinically relevant populations, such as those who have or will develop mild cognitive impairment, Alzheimer's disease, or other clinical outcomes. Second, racial and ethnic differences exist in cognitive decline in the United States (Mehta & Yeo, 2017), but the MIDUS sample is fairly homogenous relative to U.S. demographics. Future work should continue to investigate the interactive effects of the ANS on changes in cognitive functioning in diverse, pre-clinical populations who may be at risk for cognitive decline in order to explore the ANS as a modifiable therapeutic target.

4.2 | Significance

The investigation of the biomarkers for cognitive decline may have clinical implications for assessing and treating cognitive decline in an aging population. Reduced resting SNS activity coupled with increased dynamic vagal tone during challenge is associated with maintenance of cognitive function. For clinicians, it may be beneficial to assess ANS function and determine if an intervention is necessary, especially since ANS activity is a modifiable factor in health and well-being. For example, exercise is linked to improved PNS activity (Hyodo et al., 2012), reduced sympathetic activity (Mueller, 2007), and improved cognitive functioning (Erickson & Kramer, 2009). Although speculative, future research should investigate the effects of interventions that alter the interactive effects of the PNS and SNS as a possible target for bolstering cognitive functioning across the lifespan.

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CONFLICT OF INTEREST

All authors declare they have no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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