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The association of cardiac vagal control and executive functioning – Findings from the MIDUS study

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ABSTRACT

Cardiac vagal control (CVC), an index of parasympathetic contribution to cardiac regulation, has been linked to enhanced executive functioning (EF). However, findings to date have been based on small or unique samples. Additionally, previous studies assessed the CVC–EF link only during rest or recovery period from a cognitive challenge, but not during both states. In the present study, data on 817 socio-economically diverse participants were obtained from the Midlife Development in the United States (MIDUS) study. As part of this study, participants completed cognitive tests, including EF, along with laboratory-based measures of CVC during rest and following recovery from a cognitive challenge. Regression analyses adjusting for respiratory rate revealed no effect of CVC at rest or during recovery on a global index of EF. However, exploratory post-hoc analyses of the components of the global EF index revealed a significant association between faster vagal recovery and better attention-switching and response inhibition abilities, as indexed by faster reaction time to the mixed SGST. This association remained significant after controlling for demographic, clinical (BMI, diseases and medications altering cardiac autonomic functioning, etc.), and health behavior covariates (Beta = .148, $p = .010$). Our findings suggest that future studies may need to investigate the links of CVC to specific EF abilities, rather than global measures of EF. Additionally, our results highlight the importance of assessing CVC during both rest and recovery from a cognitive challenge. The authors discuss the putative neurobiological underpinning of this link, as well as suggestions for future basic and clinical research.

1. Introduction

Cardiac vagal control (CVC) reflects the input of the parasympathetic branch of the autonomic nervous system (ANS) to cardiac regulation. CVC is commonly measured using heart rate variability (HRV), an analysis of periodic beat-to-beat changes in heart rate that tend to aggregate in different frequency bands. The high-frequency band is thought to reflect fluctuations in vagal-cardiac traffic, and previous studies found that it correlates with CVC (Berntson et al., 1997). Enhanced CVC, as characterized by greater vagal reactivity and faster vagal recovery from psychological stressors, has been linked with greater ANS flexibility and an improved ability to respond to stressors (Sloan et al., 1994; Thayer and Fischer, 2009) and return to homeostasis (McEwen, 2000; Mezzacappa et al., 2001). Similarly, evidence suggests that low levels of resting CVC are associated with impaired self-regulation in both children and adults (Beauchaine, 2001; Calkins et al., 2007). Thus, CVC is an important target of investigation as it contributes to self-regulation, organization of physiological resources, and response selection in the face of challenges (McEwen, 2000).

Consistent with this view, in healthy adults greater CVC has been associated with enhanced executive functioning (EF), as well as better attention, working memory, and processing speed. In

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particular, Hansen et al. (2003) reported that among 51 male navy sailors divided to High vs. Low resting CVC (as indexed by HRV), individuals with higher CVC displayed better working memory, faster reaction time, more correct responses, and fewer attention errors. This pattern was evident only for components of the task where EF was involved. In an elegant follow-up study of 37 male sailors, CVC as indexed by HRV was found to increase with fitness training and decrease when the physical training was discontinued, with changes in cognitive performance correlating with the HRV fitness-related changes (Hansen et al., 2004). A number of other small-sample studies reported similar results, linking CVC (as indexed by HRV) to working memory, EF, and attention control (Albinet et al., 2010; Hansen et al., 2009; Schellekens et al., 2000; Middleton et al., 1999; Vincent et al., 1996). However, these findings are not universal – a large study of 5375 middle-age adults did not find associations between CVC and cognitive functioning, including EF (Britton et al., 2008). This inconsistency in findings may be due to different cognitive domains and/or different aspects of EF being assessed, a point acknowledged by Britton et al. (2008). Another explanation may be rooted in that previous studies have typically examined CVC during either rest or recovery from a cognitive challenge, but not during both.

While a number of studies support the link between higher CVC and performance on EF tasks, most studies to date have examined relatively small samples or participants with distinct backgrounds (i.e., highly-trained military personnel), bringing into question the generalizability of the findings. The only large-sample study published to date included individuals from relatively narrow occupational and SES backgrounds. This sample had relatively limited representation of low SES participants (Britton et al., 2008), an important limitation as we have previously reported that CVC at rest is associated with SES (Sloan et al., 2005). Additionally, Britton et al. (2008) assessed CVC during rest only, and did not evaluate the potential impact of medications on CVC. To the best of our knowledge, no study to date has investigated the link between EF and CVC at rest and in response to recovery from a cognitive challenge in a large representative sample. Thus, our primary aims are 1) to assess the putative link between CVC and EF in a large, socioeconomically diverse sample representative of the general population; and 2) to examine whether EF performance is differentially associated with CVC at rest vs. during the subsequent recovery period.

2. Materials and methods

2.1. Participants

Data on 817 participants were obtained from The Midlife Development in the U.S. (MIDUS), a study of the behavioral, psychological, and social factors accounting for age-related variations in health and well-being in a national sample of middle-age Americans. The data for the current study are from the second wave of MIDUS II, a 9-year follow-up of the MIDUS I cohort. MIDUS II included five large studies that were separated in time. Assessments of EF and the CVC were parts of two different studies (the Cognitive Project and the Biomarker Project, respectively). Participants first completed the EF assessments (Cognitive Project) and then, after a time lag (1–61 months; average 24.18 +/− 14.09 months), took part in the CVC assessment (Biomarker Project).

2.2. Procedures and measures

2.2.1. Assessments of executive function and the Psychophysiology Protocol

The entire MIDUS II cognitive battery was administered in a telephone interview; a detailed description of the interview process is available elsewhere (Lachman and Tun, 2008; Lachman et al., 2009; Tun and Lachman, 2008). EF was evaluated based on the EF factor previously derived (Lachman et al., 2010) from the Brief Test of Adult Cognition (BTACT) and Stop & Go Switch Task (SGST, a subtest within the BTACT; Lachman and Tun, 2008; Lachman et al., 2009; Tun and Lachman, 2006). Briefly, this factor included backward counting (speed of processing), backward digit span (working memory), category fluency (verbal ability and speed), number series (fluid intelligence/reasoning) tasks from the BTACT, and the task-switching test from the SGST. SGST is a dual EF test that includes two single-task blocks and a mixed-task block that requires alternating between two tasks, engaging key executive control functions of attention-switching and inhibitory control. In the single-task blocks, participants give a verbal response as quickly as possible to the stimulus words “RED” and “GREEN”; the first block follows a “NORMAL” (congruent) response rule (say “STOP” to “RED”, and “GO” to “GREEN”), then the second block follows a “REVERSE” (incongruent) response rule (say “GO” to “RED”, and “STOP” to “GREEN”). In the mixed-task block, the cues “NORMAL” and “REVERSE” are given at unpredictable intervals, requiring the participant to switch between the congruent and incongruent response rules midway through the block. The mixed SGST task requires EF of both attention-switching and inhibitory control, and it is indexed by the average of the switch & non-switch trials (Tun and Lachman, 2008). While BTACT provided accuracy measures only, SGST provided both accuracy and latency (e.g., reaction time in ms) measures. For the computation of EF factor, attention-switching/response inhibition time was multiplied by −1 to indicate greater values represent faster response time. To demonstrate that the participant adequately understood and engaged in the task, a minimum of 75% task accuracy was required for inclusion of data.

The Psychophysiology Protocol was administered in the morning after a light breakfast with no caffeinated beverages. ECG electrodes were placed on the left and right shoulders, and in the left lower quadrant. Respiration bands were put on chest and abdomen. The participant was seated, and a keypad for responding to the stress tasks was secured in a comfortable position relative to the dominant hand. The stressors used included a mental arithmetic task (Turner et al., 1986) and the Stroop color–word conflict task. Importantly, these tasks were used only as a stressor, not as an EF measure. Both stressors were computer-administered and their order was counterbalanced. After receiving the instructions, participants practiced the stressor tasks. Next, there were a first calibration period (up to 10 min), checking signal quality (up to 10 min), and a second calibration period (up to 4.67 min). Next, the baseline functioning was measured for 11 min, followed by the first stressor, a recovery period, the second stressor, and the second recovery period. All stressor and recovery periods lasted 6 min (see Fig. 1).

CVC was evaluated using high-frequency (HF) power of HRV (Berntson et al., 1997). Following previously reported procedures (Shcheslavskaya et al., 2010), analog ECG signals were digitized at 500 Hz by a National Instruments A/D board and passed to a microcomputer for collection. The ECG waveform was submitted to an R-wave detection routine implemented by proprietary event detection software, resulting in an RR interval series. Errors in marking R-waves were corrected interactively following established procedures (Dykes et al., 1986). Natural log transformation was performed prior to the analysis. Chest and abdominal respiration signals were submitted to proprietary software that produced minute-by-minute means of respiratory rate (Crowley et al., 2011; Sloan et al., 2001).

2.2.2. Assessment of cardiac vagal control at rest and recovery

To obtain stable response estimates for each period (e.g., rest, challenge, recovery), and to enhance the reliability of our findings,

Seated Resting Baseline	Psychological Stressor (Math or Stroop Task) *	Recovery 1	Psychological Stressor (Math or Stroop Task) *	Recovery 2
(11 minutes)	(6 minutes)	(6 minutes)	(6 minutes)	(6 minutes)

* The order of the tasks was counterbalanced.

Fig. 1. Psychophysiology Protocol.

we followed an established procedure recommended in the psychophysiological literature (Kelsey et al., 2007) and averaged ln HF data for minutes 5–10 of the rest period, both challenges, and the associated recovery periods (Crowley et al., 2011). Vagal recovery was evaluated as a difference between the recovery period and the challenge period. Specifically, a vagal recovery score was computed by subtracting aggregated ln HF during the mental arithmetic and Stroop challenges from the aggregated ln HF during the two associated recovery periods. As CVC decreases in response to stress and increases during recovery (Mezzacappa et al., 2001), a greater recovery score represents larger post-stress increases in ln HF.

2.3. Statistical analyses

All analyses were performed using SPSS (ver. 18). The data were analyzed using multiple linear regressions with the CVC (rest and recovery score) as a predictor of EF. All analyses controlled for the time lag between the assessments of EF and the Psychophysiology Protocol. We also adjusted for the effects of the three categories of covariates: demographic (age, sex, education), clinical (BMI, menopausal status, diseases and medications altering cardiac autonomic control), and health behaviors (exercise, smoking). Menopausal status was classified as pre-, peri- and post-menopausal, with pre-menopausal status serving as a reference. Diseases and medications that can alter CVC were entered in the analysis as a covariate. Specifically, we created a dummy variable that categorized the participants as either 1) having at least one of these diseases *or* taking at least one of these medications; or 2) disease- *and* medication-free. This dummy "disease/medications" variable was then entered in the analysis. Three types of exercise/physical activity were evaluated separately in MIDUS II: the participants reported how many hours per week they spent performing vigorous, moderate, and light physical activity or exercise. Therefore, we created three continuous exercise/physical activity variables, with participants who did not report any physical activity being scored as zero. For smoking status, we created three dummy variables classifying participants' status; two were entered in the model (current smoker and ex-smoker), while the third (never smoked) was used as a reference.

As HRV is influenced by respiration, we conducted all analyses before and after adjusting for respiratory rate. To estimate the variance in ln HF that cannot be explained by the effect of respiration, we conducted within-subject regression analyses using respiratory rate as a predictor of ln HF on a minute-by-minute basis (Sloan et al., 2001). Specifically, for each participant we regressed respiratory rate for each 1-min epoch on ln HF for the same epoch (controlling for the effect of the rest, challenge, and recovery periods). We used the resulting unstandardized residual scores as an estimate of the variance in ln HF that cannot be explained by the effect of respiratory rate. These residuals were then used to compute vagal recovery scores.

We tested separately two models for 1) rest-related CVC; and 2) vagal recovery. To control for Type I Error, we used Bonferroni adjustment and set alpha level at .05/2 = .025. The analysis was conducted in four steps – we entered 1) CVC as a predictor of EF (adjusting for the time lag between the assessments of EF and the Psychophysiology Protocol); 2) demographic covariates; 3) clinical covariates; and 4) health behavior covariates. We replicated the analysis in the subsets of the participants who had diseases/took medications affecting CVC ($n = 609$) and the participants who did not have these disease/take these medications ($n = 208$).

3. Results

Of the 4512 participants for whom cognitive assessments were available and the 1255 Psychophysiology Protocol participants, a total of 817 participants had valid HRV data (rest, reactivity, and recovery), completed the EF tasks, had data on the nine covariates described above, and met the 75% response accuracy criteria. Table 1 provides demographic and clinical characterization of these 817 participants. Table 2 provides descriptive statistics for the participants' performance on the EF tasks and global EF factor.

3.1. Executive functioning and rest CVC

Table 3 presents analyses of the associations between rest CVC and EF global factor. Regression analyses controlling for the time lag between the assessments of EF and the Psychophysiology Protocol and adjusting for respiratory rate showed a significant association between rest CVC and EF global factor (Beta = .134, $p = .000$). However, the addition of the demographic covariates (age, sex, education) to the model eliminated the significance of this association. Further addition of the clinical (BMI, menopausal status, diseases/medications) and health behavior (exercise, smoking) covariates did not change these results.

To evaluate whether rest CVC is associated with specific component of the EF global factor, we conducted exploratory post-hoc analyses of the associations between rest CVC and components of the EF global factor. Regression analyses controlling for the time lag between the assessments of EF and the Psychophysiology Protocol and adjusting for respiratory rate showed association between rest CVC and fluid intelligence/reasoning, working memory, speed of processing and task-switching. However, the addition of the demographic, clinical, and health behavior covariates eliminated the significance of this association. To evaluate whether the presence of medication- or cardiac-altering diseases had an impact on the rest period findings, we conducted a post-hoc regression analyses for individuals with and without the presence cardiac- or medication-altering diseases, controlling for the time lag between the EF assessments and the Psychophysiology Protocol and adjusting for respiratory rate. The results indicated a significant association between rest CVC and EF global factor (Beta = .126, $p = .002$), speed of processing (Beta = .108, $p = .009$), and task-switching (Beta = .082, $p = .046$) among those participants who had diseases/took medications affecting CVC ($n = 609$). However, the addition of the demographic covariates to the model eliminated the significance of this association. Further

Table 1
The sample's demographic and clinical characteristics.

		N (%)	Mean (SD)
Age[a]		817 (100%)	57.11 (11.15)
Sex	Male	361 (44.2%)	N/A
	Female	456 (55.8%)	
Education	Some high school (no diploma/no GED)	26 (3.2%)	N/A
	Graduated from high school or received GED	165 (20.2%)	
	1–2 Years of college, no degree	136 (16.6%)	
	3 or More years of college, no degree	33 (4%)	
	Graduated from 2-year college, vocational school associate degree	65 (8%)	
	Graduated from a 4- or 5-year college, or bachelor degree	194 (23.7%)	
	Some graduate school	37 (4.5%)	
	Master's degree	123 (15.1%)	
	PhD, EdD, MD, LLB, JD, or other professional degree	35 (4.3%)	
BMI	Body mass index	817 (100%)	29.05(5.92)
Diseases altering cardiac autonomic functioning	High blood pressure	255 (31.2%)	N/A
	Heart disease	74 (9.1%)	
	Diabetes	79 (9.7%)	
	Circulation problems	51 (6.2%)	
	TIA or stroke	22 (2.7%)	
	Depression	157 (19.2%)	
	Cholesterol problems	346 (42.4%)	
	Asthma	91 (11.1%)	
	Emphysema/COPD	25 (3.1%)	
	Thyroid disease	101 (12.4%)	
	Have any of the diseases listed above	580 (71%)	
Medications altering cardiac autonomic control	Cardiac vagal control	250 (30.6%)	N/A
	Cardiac sympathetic control	104 (12.7%)	
Take any of the medications listed above	Yes	538 (65.9%)	N/A
	No	279 (34.1%)	
Have any of the diseases/take any of the medications listed above	Yes	609 (74.5%)	N/A
	No	208 (25.5%)	
Menopausal status	Pre-menopausal	130 (15.9%)	N/A
	Peri-menopausal	38 (4.7%)	N/A
	Post-menopausal	287 (35.1%)	N/A
Smoking	Never	461 (56.4%)	N/A
	Current smoker	87 (10.6%)	
	Ex-smoker	269 (32.9%)	
Exercise/physical activity (hours per week per person)[b]	Vigorous	817 (100%)	.98(3.01)
	Moderate	817 (100%)	2.77(5.56)
	Light	817 (100%)	1.72(4.48)

$N = 817$.
[a] As the Cognitive Functioning and Biomarker studies were conducted at separated times, analyses were conducted based on participants' age at the time when the psychophysiology data were collected (e.g., the biomarker study). For comparisons of these 817 participants to the rest of the Cognitive Functioning study sample ($N = 3994$), we used their age at the time when the cognitive assessments were performed (e.g., the Cognitive Functioning study).
[b] Participants who did not report a given type of physical activity were scored as zero.

addition of the clinical and health behaviors covariates did not change these results. There were no associations between at rest CVC and EF among participants who did not have diseases/take medications affecting CVC ($n = 208$).

3.2. Executive function and vagal recovery

A regression analyses controlling for the time lag between the assessments of EF and the Psychophysiology Protocol and adjusting for respiratory rate showed no association between vagal recovery score and EF evaluated as a global factor. Adding the demographic, clinical, and health behavior covariates to the model did not change this association.

To evaluate whether vagal recovery is associated with specific components of the EF global factor, we conducted exploratory post-hoc analyses of the associations between vagal recovery score and the five components of the EF global factor. Regression analyses controlling for the time lag between the assessments of EF and the Psychophysiology Protocol and adjusting for respiratory rate showed significant association between vagal recovery score and task-switching (Beta = .157, $p = .008$). This association remained significant after adding the demographic, clinical, and health behavior covariates (Beta = .148, $p = .010$). All the other domains of the EF global factor were not associated with vagal recovery score.

To evaluate whether use of medications- or cardiac-altering diseases influenced the recovery findings, we conducted a post-

Table 2
Mean, median, mode, and range of scores for the cognitive task measures comprising the executive functioning general factor.

Cognitive tasks	Mean (SD)	Median	Mode	Range
Working memory: digits backward span (highest number of digits recalled (BTACT))	5.08 (1.39)	5	4	0–8
Speed of processing: backward counting (total number of digits counted correctly (BTACT))	40.01 (11.12)	39	31	13–81
Verbal ability: category fluency (total number of unique responses (BTACT))	20.05 (5.80)	20	19	5–39
Fluid intelligence/reasoning: number series (total number of items reported correctly (BTACT))	2.61 (1.52)	3	3	0–5
Attention switch/response inhibition: SGST mixed task (median reaction time for the averaged switch & non-switch trials (SGST))	1.04 (.20)	1	.86	.63–2.30

$N = 817$.

Table 3
Associations of cardiac vagal control with executive functioning during the baseline and recovery periods.

		Baseline		Recovery	
		β	*p*	*β*	*p*
Step 1 – univariate analysis (controlling for the time lag between the Biomarker and Cognitive projects)					
Executive functioning: global factor		**.134**	**.000**	−.029	.625
Components of the executive functioning factor	Verbal ability	.069	.054	.057	.338
	Fluid intelligence/reasoning	**.098**	**.006**	−.040	.506
	Working memory	**.082**	**.020**	−.027	.650
	Speed of processing	**.097**	**.006**	−.012	.841
	Task-switching	**.089**	**.011**	**.157**	**.008**
Step 2 – after inclusion of demographic covariates					
Executive functioning: global factor		.020	.536	.023	.658
Components of the executive functioning factor	Verbal ability	−.016	.643	.046	.403
	Fluid intelligence/reasoning	.033	.329	−.043	.433
	Working memory	.044	.225	−.034	.565
	Speed of processing	−.013	.698	−.008	.875
	Task-switching	.014	.688	**.153**	**.007**
Step 3 – after inclusion of clinical covariates					
Executive functioning: global factor		.009	.785	.015	.770
Components of the executive functioning factor	Verbal ability	−.021	.552	.044	.434
	Fluid intelligence/reasoning	.026	.440	−.048	.382
	Working memory	.036	.334	−.041	.492
	Speed of processing	−.022	.512	−.014	.800
	Task-switching	.008	.817	**.148**	**.009**
Step 4 – after inclusion of health behavior covariates					
Executive functioning: global factor		.013	.677	.018	.721
Components of the executive functioning factor	Verbal ability	−.018	.599	.043	.444
	Fluid intelligence/reasoning	.034	.318	−.054	.327
	Working memory	.039	.290	−.025	.673
	Speed of processing	−.022	.511	−.012	.828
	Task-switching	.010	.786	**.148**	**.010**

$N = 817$; scores adjusted for respiratory rate; demographic covariates – age, sex, education; clinical covariates – BMI, menopausal status, diseases and medications that influence cardiac functioning; health behavior covariates – smoking, physical exercise; verbal ability – category fluency; fluid intelligence/reasoning – number series; working memory – digits backward span; speed of processing – backward counting; task-switching – median reaction time for the averaged SGST switch & non-switch trials.

hoc regression analyses for individuals with and without the presence cardiac- or medication-altering diseases, controlling for the time lag between the EF assessments and the Psychophysiology Protocol and adjusting for respiratory rate. The results indicate that marginally significant associations between task-switching and vagal recovery score were observed for those participants who had diseases/took medications affecting CVC (Beta = .127, $p = .059$) and those participants who did not have these diseases/take these medications (Beta = .233, $p = .055$). This finding remained marginally significant after controlling for the demographic, clinical, and health behaviors covariates (Beta = .122, $p = .061$; Beta = .242, $p = .049$, respectively). There was no relationship between the EF global factor or other components and vagal recovery score for the both parts of the sample.

4. Discussion

The present study is the first to investigate the relationship between CVC and EF at rest and during recovery from a laboratory challenge in a large, socioeconomically diverse sample. Our findings indicate that faster vagal recovery is associated with enhanced performance on EF tasks involving attention-switching/response inhibition. There were no associations between vagal recovery and EF evaluated as a global factor or its other components. Interestingly, participants' performance on the SGST and BTACT indicated dissociation between tasks that involve EF (and to a smaller degree, processing speed reaction time), and the simpler one that indexes basic processing speed alone. These findings are consistent with previous reports that linked higher HRV (better CVC) with better performance on tasks involving EF (Hansen et al., 2003, 2004).

The dissociation between CVC and performances on attention-switching/response inhibition vs. the global EF factor suggest that effective vagal recovery from challenge may not relate equally to all EF abilities (Miyake et al., 2000). These findings are consistent with previous reports – using confirmatory factor analysis, Miyake et al. (2000) found that three components of EF (shifting, updating, and, inhibition) displayed moderate correlations, but were clearly separable. Further structural equation modeling suggested that the three components contributed differentially to performance on complex executive tasks. The authors concluded that EF comprises of "separable but related functions that share some underlying commonality" (Miyake et al., 2000, p. 88). Data from developmental studies further support this view, indicating that components of EF develop unevenly throughout childhood (Jurado and Rosselli, 2007). These findings are also consistent with data on broader cognitive functioning – a large meta-analysis of 29 studies with 2049 participants found that aerobic exercise, which is closely linked to CVC, significantly improved EF abilities including attention/processing speed, as well as declarative memory, but not working memory (Smith et al., 2010).

The lack of associations between CVC and working memory during rest and recovery periods are in contrast to the results published by Hansen et al. (2003). One explanation for this discrepancy may be rooted in that participants in the Hansen study had HRV assessed during the working memory task, while in our study the CVC and cognition measures were evaluated on separate occasions, in some cases several years apart. Alternatively, the lack of association may reflect limited working memory instrument sensitivity. Relative to the task we used to assess attention-switching/response inhibition domain of EF, the BTACT had a relatively narrow range of scores, with the majority of participants

scoring in the 3–7 range (mean = 5.08, SD = 1.39), potentially minimizing the possibility of identifying significant associations. Finally, differences in sample size may account for these differences.

The association between CVC during recovery and attention-switching/response inhibition invites speculation about the potential shared neurobiology underlying this link. Effective performance on EF tasks such as the SGST, requires participants to inhibit their natural inclination to respond to the prepotent stimulus of RED and GREEN with STOP and GO responses, respectively. A number of researchers have hypothesized about cortical-subcortical circuitry involved in inhibitory processes (Masterman and Cummings, 1997) and these circuits have been tied to CVC (Thayer and Lane, 2000). In general, inhibitory processes associated with EF are lateralized primarily to the right hemisphere (Garavan et al., 1999) and a number of animal and human imaging studies have implicated the insula and inferior frontal gyrus (IFG) in contributing to behavioral inhibitory processes during EF tasks (Kenner et al., 2010; Chikazoe, 2010; Lerner et al., 2009). Inhibitory modulation of cardiac function is similarly lateralized primarily to the right hemisphere (Ter Horst and Postema, 1997), with the insular cortex involved in cortical control of cardiovascular functioning (Nagai et al., 2010; Peters et al., 2009). Results from animal studies suggest that the insular cortex influences the cardiac baroreflex through a modulation of parasympathetic output (Saleh and Connell, 1998; Hanamori, 2005). In human studies, a number of authors have reported a link between CVC and insular cortex activity (Lane et al., 2009; Critchley et al., 2005). Similarly, a significant association has been found between right anterior insular cortex gray matter density and aerobic capacity (Peters et al., 2009; Gondoh et al., 2009), which is linked with CVC. In another study, right but not left insular regional Cerebral Blood Flow (rCBF), were significantly related to blood pressure increase and ratings of perceived exertion during exercise, with the magnitude of insular activation varying with the intensity of aerobic exercise (Williamson et al., 1999). Altogether, these findings suggest that the insular cortex may underlie the link between behavioral inhibition and CVC.

Our results have a number of potential implications for basic research. First, our findings that CVC is associated with performance on attention-switching/response inhibition, but not EF overall suggest that future studies may need to investigate links between CVC and specific EF abilities rather than global measures of EF. Second, our findings of differences in associations between cognitive performance and CVC at rest and during recovery from cognitive challenge highlight the importance of examining CVC under both conditions. Because of the post-hoc nature of these findings, these results need to be replicated. However, if confirmed, our findings may clarify some of conflicting results in the literature and the difference between our findings and results from the only other large study on CVC and EF (Britton et al., 2008). In that study, cardiac autonomic data were collected from participants during rest only. Additionally, the author reported using a test that does not assess EF in detail. Future studies will also need to confirm the putative role of the IFG and insular cortex in linking CVC and performance on attention-switching/response inhibition EF tasks.

Our results also have potential implications for clinical research. A growing literature supports the positive impact of aerobic exercise on both CVC and cognitive functioning, including EF (Sloan et al., 2009; Smith et al., 2010; Albinet et al., 2010; Colcombe and Kramer, 2003), suggesting a candidate physiological mechanism linking CVC with cognitive functioning. Thus, our findings may have implications for improving cognitive functioning in clinical populations in which cognitive deficits are prevalent. For example, individuals with schizophrenia display a broad range of cognitive impairments across several cognitive domains, including EF (Nuechterlein et al., 2004). Additionally, many individuals with schizophrenia display a relatively sedentary lifestyle (Daumit et al., 2005) and have been found to have low HRV, characterized by poor vagal input (Bär et al., 2005; Kimhy et al., 2010). Individuals with schizophrenia have also been found to display slower vagal recovery following cognitive challenges compared to their first-degree relatives and healthy controls (Castro et al., 2008, 2009). As pharmacological interventions targeting cognitive functioning in this population have proven disappointing (Buchanan et al., 2011; Javitt et al., 2012), and preliminary findings indicate that aerobic exercise may improve cognitive functioning in this population (Pajonk et al., 2010), future studies will be needed to confirm the putative positive impact of aerobic exercise on cognitive functioning, including EF, in individuals with schizophrenia.

The current findings are not without limitations. One limitation is the time gap between the assessment of the CVC and cognitive tests, which in some cases was several years apart. The MIDUS project was clearly not designed specifically to assess the association between CVC and EF. At the same time, the extensive data collected as part of this project also represents a rare opportunity to investigate the putative link between CVC and EF in a large, diverse, and well-characterized sample. This point is particularly relevant given the relative lack of studies with large and representative samples focusing on this issue. Thus, in the present manuscript, we took advantage of this unique opportunity. While we attempted to control statistically for the time gaps, such a gaps may have obscured or weakened potential associations between CVC and EF. Another potential limitation is the lack of information about current state of menstrual cycle among female participants. Our group (McKinley et al., 2009) have found that the phase of the menstrual cycle has a distinct impact on HRV, thus potentially influencing the associations between the CVC and EF performance. Finally, a number of nutrients may have influence on vagal tone (e.g., Omega 3 fatty acids). Information about consumption of such nutrients was not available.

Conflict of interest

None of the authors had any conflict of interest.

Contributors

Drs. Kimhy and Crowley managed the literature searches and wrote the first draft of the manuscript. Dr. Crowley conducted the statistical analyses.

Dr. McKinley is a Co-Investigator for The Biomarker study (Project 4) of the MIDUS study. Dr. McKinley coordinated processing of the cardiovascular and respiratory data for the Psychophysiology Protocol (administered as part of Project 4), contributed to the statistical analyses and interpretation of the findings for the manuscript, and provided feedback for the multiple drafts.

Dr. Burg contributed to the statistical analyses and interpretation of the findings for the manuscript, and provided feedback for the multiple drafts.

Dr. Lachman is a Principal Investigator for The Cognitive Functioning study (Project 3) of the MIDUS study. Dr. Lachman coordinated the administration and processing of executive function assessments, contributed to the statistical analyses and interpretation of the findings for the manuscript, and provided feedback for the multiple drafts.

Dr. Tun is a Co-Investigator for The Cognitive Functioning study. Dr. Tun coordinated the administration and processing of executive function assessments, contributed to the statistical analyses and

interpretation of the findings for the manuscript, and provided feedback for the multiple drafts.

Dr. Ryff is a Principal Investigator for the MIDUS study and a Co-Leader for The Biomarker study. Dr. Ryff contributed to the statistical analyses and interpretation of the findings for the manuscript, and provided feedback for the multiple drafts.

Dr. Seeman is a Co-Leader for The Biomarker study. Dr. Seeman coordinated collection of cardiovascular and respiratory data for the Psychophysiology Protocol, contributed to the statistical analyses and interpretation of the findings for the manuscript, and provided feedback for the multiple drafts.

Dr. Sloan is a Co-Investigator for The Biomarker study. Dr. Sloan contributed to the statistical analyses and interpretation of the findings for the manuscript, and provided feedback for the multiple drafts.

All authors contributed to and have approved the final version of the manuscript.

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The sponsors had no role in the design and conduct of the study (collection, management, analysis) nor in the interpretation of the data. The sponsors have not seen the manuscript.

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