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Metabolic Risk in Older Adults is Associated with Impaired Sustained Attention

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Objective: Metabolic syndrome (MetS), the presence of three or more cardiovascular risk factors, has been associated with subtle and diffuse neural compromise but has not been consistently associated with cognitive dysfunction. Sustained attention is a fundamental cognitive operation that relies on multiple brain networks and is impaired in a broad array of neurologic conditions. We examined whether a well-validated measure of sustained attention would be sensitive to vascular risk, as compared with more standard neuropsychological measures of attention and executive functioning. ***Method:*** We assessed vascular risk factors (VRFs; blood pressure, waist circumference, cholesterol, glucose, and triglycerides) in 93 middle-to-older aged adults (45–75 years). MetS was defined based on current guidelines from the National Cholesterol Education Program Adult Training Program (NCEP ATP III). Participants were grouped according to number of VRFs: high risk (MetS; 3+ VRFs; $N = 32$), medium risk (1 or 2 VRFs; $N = 35$), and low risk (0 VRFs; $N = 26$). All participants underwent a neuropsychological battery of tests measuring executive functioning. Participants also performed the gradual-onset continuous performance task (gradCPT), a measure of sustained attention. ***Results:*** There was a significant main effect of VRF group on sustained attention performance; participants with lower vascular risk were better able to sustain attention. No significant effects were detected on standard neuropsychological tests of executive function. ***Conclusion:*** Our results suggest that the gradCPT is sensitive to the potentially negative effects of MetS on subtle aspects of neurocognitive functioning.

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General Scientific Summary
In this study, we examined the relationship between vascular risk factors and attention/executive functioning. We found that greater vascular risk was associated with significantly worse sustained attention. Our results suggest the gradCPT may be sensitive to the subtle effects of vascular risk and metabolic syndrome on cognition.

Keywords: metabolic syndrome, sustained attention, executive function, vascular risk factors

Risk factors for cerebrovascular disease, such as hypertension and high cholesterol, have become increasingly more prevalent in the adult population in the past several decades. Such vascular risk factors (VRFs) rarely occur in isolation, and in fact, metabolic syndrome (MetS), the presence of three or more VRFs (high blood pressure, high cholesterol, abnormal fasting glucose, and obesity), has become a major public health concern for the United States and nations abroad (Grundy et al., 2005). A recent analysis of a large, nationally representative sample has shown prevalence of MetS in the general population to be 34%, and as high as 50% in older adults (Aguilar, Bhuket, Torres, Liu, & Wong, 2015). In affected individuals, MetS significantly increases all-cause mortality rate, and risk of cardiovascular disease related mortality (Malik et al., 2004). Poor cardiovascular health in midlife has also been shown to more than double the risk of cognitive decline and dementia in older adulthood, with vascular dementia (VaD) and vascular-related cognitive impairment as the most prominent and common MetS related manifestation (González et al., 2017; Raffaitin et al., 2009).

There is compelling evidence linking MetS to impairments in global brain health, even before the development of measurable cognitive impairment. Studies have shown reduced gray matter volume (Yates, Sweat, Yau, Turchiano, & Convit, 2012), decreased white matter integrity (Sala et al., 2014), and altered connectivity of resting state functional magnetic resonance imaging (fMRI; Musen et al., 2012) in patients with MetS. Findings have also suggested regional specificity of the effects of MetS, predominantly in frontal, temporal and parietal brain regions (Leritz et al., 2010; Schwarz et al., 2018). Not surprisingly, MetS has also been associated with reduced cognitive function in multiple domains (Yates et al., 2012). Impaired executive functioning is the most commonly reported deficit associated with MetS, although findings are mixed, with some cross-sectional studies reporting no effects (Haley et al., 2010; Tournoy et al., 2010). More specifically, Haley et al. (2010) found no group differences in global cognitive functioning, memory, language, and psychomotor performance among middle-aged adults. In a large sample of middle-to-older aged men, Tournoy et al. (2010) found no relationship between metabolic syndrome and cognitive impairment. One possibility for the lack of consistency with regard to cognition and MetS is that change across broad cognitive domains is often difficult to detect before decline is pronounced, especially in the absence of overt neurologic illness. It is possible that more subtle aspects of cognition are affected by VRFs and MetS.

Sustained attention is a foundational aspect of cognition that is seen as a "cognitive gatekeeper" for important processes such as learning, memory, and overall executive functioning (Fortenbaugh et al., 2015). Because sustained attention underlies many fundamental cognitive operations, it is a uniquely important subcomponent of executive functioning; responsible for a variety of everyday functional tasks, from effectively accomplishing work or school activities (Steinmayr, Ziegler, & Träuble, 2010) to driver safety (Yanko & Spalek, 2013) to effective social communication (Bennett Murphy, Laurie-Rose, Brinkman, & McNamara, 2007). Further, sustained attention relies on the coordination of a wide range of brain regions. This was demonstrated in a recent meta-analysis which found a number of brain regions consistently activated during sustained attention (Langner & Eickhoff, 2013). These brain regions fell within the dorsal attention network (DAN), as well as several other task-positive networks that are not exclusively thought to be involved in attentional control, such as the ventral attention network (VAN), salience network (SN), default mode network (DMN), and executive control network (ECN). Thus, sustained attention may be particularly sensitive to distributed and subtle neural compromise caused by vascular disease and could explain the inconsistencies relating vascular risk to more specific cognitive domains. Though sustained attention has been shown to be worse in diseases related to MetS (e.g., Type 1 diabetes; van Dijk et al., 2014), and high blood pressure (Tarraf et al., 2017; Van Vliet, Hilt, Thijs, & Van Dijk, 2016), to our knowledge no study has shown a relationship between MetS and sustained attention. Development of a behavioral task sensitive to vascular-related sustained attention dysfunction could lead to earlier detection of neurovascular disease and more opportunity for early interventions.

The gradual continuous performance task (gradCPT) is a well validated measure of sustained attention and has been shown to activate functional brain networks theorized to be most at risk by vascular dysfunction (Esterman, Noonan, Rosenberg, & Degutis, 2013; Esterman, Rosenberg, & Noonan, 2014; Fortenbaugh et al., 2015; Fortenbaugh, Rothlein, McGlinchey, DeGutis, & Esterman, 2018; Jacobs et al., 2013; Riley, Esterman, Fortenbaugh, & DeGutis, 2017). The gradCPT has been shown to be sensitive to deficits in attentional control related to aging (Fortenbaugh et al., 2015), as well as a range of neuropsychiatric impairments (Auerbach et al., 2014; DeGutis et al., 2015; Dutra, Marx, McGlinchey, DeGutis, & Esterman, 2018; Esterman et al., 2013; Rosenberg et al., 2016). The main innovation of the gradCPT is the gradual fading of stimulus image into the next, replacing abrupt onsets and offsets of each stimulus. This removes onset/offset-induced exogenous cueing that signal trial-to-trial stimulus changes seen in similar go/no-go sustained attention paradigms such as the sustained attention to response task (SART; Fortenbaugh, Degutis, & Esterman, 2017).

In the current study, we examined sustained attention in a sample of individuals with a range of vascular risk using the gradCPT. We hypothesized that deficits in sustained attention would be associated with a higher number of VRFs. We further anticipated deficits related to elevated VRFs could be more apparent in sustained attention than other related domains of executive functioning, as assessed by standard neuropsychological tests.

Method

Study Design and Participants

One hundred middle-to-older aged adults who were part of the Cerebrovascular Integrity and Risk for Cognitive decline in Aging (CIRCA) study ($M = 61.94$ years, $SD = 9.46$) participated in this study. CIRCA is a cross-sectional study designed to examine the effect of VRFs on cognitive function. Participants were enrolled from direct clinic recruitment via the Department of Veterans Affairs Healthcare Services to target those at high risk for MetS, as well as through advertisement in the greater Boston, MA metropolitan area. Inclusion criteria required participants to be English speakers and between the ages of 45–90. Exclusion criteria encompassed significant medical disease (e.g., overt cardiovascular, hepatic, or renal disease), neurological disorders (e.g., Parkinson's disease or dementia), prior major surgery (e.g., brain or cardiac surgery), head trauma (e.g., loss of consciousness for >30 min), history of severe or current psychiatric disorders (e.g., schizophrenia or major depressive disorder), history or current diagnosis of drug abuse or dependence, or any contraindication to MRI. Though MRI scans were performed, they are not analyzed in the current study.

Data collection was completed over a period of 4 years from 2014–2018. Participants completed study visits over 1 or 2 days, depending on their personal choice and schedules. Each participant underwent neuropsychological testing in a quiet room, administered by a research assistant who was trained by a board-certified neuropsychologist (EL).

The Institutional Review Board of the Department of Veterans Affairs (VA) Boston Healthcare System approved this protocol and all participants provided informed consent before study procedures.

Metabolic Syndrome Criteria

Based on National Cholesterol Education Program Adult Treatment Program (NCEP ATP-III) guidelines, participants were considered to have metabolic syndrome if they met three or more of the following criteria: (a) elevated waist circumference $\geq$102/88 cm or $\geq$40/35 in. men/women; (b) elevated triglycerides $\geq$150 mg/dL or drug treatment for elevated triglycerides; (c) reduced high density lipid cholesterol (HDL-C) $<$ 40/50 mg/dL in men/women or drug treatment for reduced HDL-C; (d) elevated systolic BP $\geq$130 mmHg or diastolic BP $\geq$85 mmHg or drug treatment for hypertension; and (e) elevated fasting plasma glucose $\geq$100 mg/dL or drug treatment for elevated glucose (Grundy et al., 2005). Participants were grouped according to number of vascular risk factors; high risk (MetS; 3 + VRFs), medium risk (1 or 2 VRFs), and low risk (0 VRFs).

Gradual-Onset Continuous Performance Task

The gradCPT is a go/no-go continuous performance task designed to measure sustained attentional control. During the 4-min task, participants were shown a series of gray-scale scene images that gradually transition from one to the next approximately every 800 ms using linear pixel-by-pixel interpolation. The gradCPT requires participants to respond via button press to frequently occurring city images (90% of stimuli) and withhold their response to rare mountain images (10% of stimuli). In addition to the gradual and overlapping nature of the task, the rapid pace encourages a consistent reaction time (RT), as RTs that are too fast (leading to errors of commission to rare mountains) and too slow (leading to errors of omission) are associated with worse accuracy. This abbreviated 4-min version is identical to a previous experiment with a large normative sample size of over 10,000 participants, for which performance is well characterized across the life span (Fortenbaugh et al., 2015; Riley et al., 2017; Rothlein et al., 2018). Data exclusion criteria followed the previous protocol and data were discarded from any participants who had a prolonged period (30 s or more) without a response, as this indicates noncompliance with task instructions. This excluded seven participants from our sample, with 93 remaining. Before the task, each participant was given three 30 second practice sessions.

Measures of Sustained Attention Ability

The primary measure of sustained attention ability on the gradCPT is accuracy (d'; Fortenbaugh et al., 2015). A secondary measure of sustained attention ability is RT variability (coefficient of variation, CV). Each was calculated using custom MATLAB (MathWorks, Inc., Natick, MA) scripts. Specifically, d' is calculated with signal detection analyses to quantify the ability to discriminate between targets/nontargets independent of response strategy. CV, a measure of RT variability, is calculated from correct responses to nontargets using the standard deviation of RT divided by the mean RT (Macmillan & Creelman, 1991). Higher CV is indicative of high RT variability, and has been shown to be associated with poorer sustained attention ability (Fortenbaugh et al., 2015).

Neuropsychological Assessment

All participants underwent a comprehensive battery of neuropsychological measures to assess broad domains of cognition. The following measures were administered: Digit Span subtest from the Wechsler Adult Intelligence Scale-III (WAIS-III; Wechsler, 1997), the Stroop Color Word Test (SCWT; Spreen & Strauss, 1998), Trail Making parts A & B (Spreen & Strauss, 1998) Controlled Oral Word Association (COWA; Spreen & Strauss, 1998), the Logical Memory subtest from the Wechsler Memory Scale-Third Edition (Wechsler, 1997), the California Verbal Learning Test-Second Edition (CVLT; Delis, Kaplan, & Kramer, 2001), and the Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 2010). From this battery, we chose the following measures of executive function (working memory, inhibitory control, and task switching, respectively) to examine as a comparison with measures of the gradCPT: Digit Span sequencing (from the WAIS-III; Wechsler, 1997), the Stroop Color Word Test (SCWT; Spreen & Strauss, 1998), and Trail Making parts A & B (Spreen & Strauss, 1998). Specific measures used were Digit Span Sequencing total (raw score), Color Word Interference: Inhibition (Total Time), and Trails: Number/Letter Switching (Total Time).

Statistical Analysis

First, we assessed whether gradCPT performance differed based on vascular risk group (zero, one or two, three or more) with a one-way analyses of variance including several covariates (Keselman et al., 1998). Post hoc comparisons using the Tukey's honest significant difference (HSD) test were conducted to further assess differences across vascular risk groups. Second, we used Pearson partial correlations to examine whether behavioral performance was associated with the number of qualifying VRFs, while controlling for a number of covariates. Finally, we assessed each VRF individually for behavioral differences again using the same analysis of variance (ANOVA) approach. These analyses were repeated for the neuropsychological measures of the subdomains of executive functioning (Miyake et al., 2000): working memory, inhibitory control, and task switching. In our analyses of variance and Pearson correlations with performance variables, covariates included age, gender, and education because of these variables' relationship to number of VRFs and vascular risk groups.

Results

Participant characteristics are described in Table 1, differentiated by qualification for number of VRFs. It should be noted there were age differences across groups, $F(2, 90) = 3.56$, $p = .03$, but no differences in level of education, $F(2, 90) = 2.22$, $p = .11$, or gender, $F(2, 90) = 1.39$, $p = .25$. There was also a relationship between the number of VRFs and gender ($r = -.21$, $p = .045$), and level of education ($r = -.21$, $p = .046$), while age ($r = .19$, $p = .074$) was nonsignificant. Depression, assessed by the Beck Depression Index (Beck, Steer, & Brown, 1996), was not significantly different across groups, $F(2, 89) = .565$, $p = .57$, nor was it associated with number of VRFs ($r = .08$, $p = .44$). Thus, age, gender, and education were included as covariates in all subsequent analyses.

Differences in Sustained Attention Based on Metabolic Syndrome Criteria

An ANOVA of our primary measure of sustained attention (d') with age, gender, and education included as covariates showed the effect of vascular group was significant ($F(2, 87) = 3.60$, $p = .03$, $\eta_p^2 = .076$; Figure 1). This was driven by the best performance in those with no VRFs, intermediate performance in those with one or two VRFs, and worst performance in those with metabolic syndrome. Post hoc comparisons using the Tukey's HSD test indicated that d' for those with VRFs ($M = 3.27$, $SD = .70$) was significantly different than those who had three or more VRFs ($M = 2.68$, $SD = .91$). However, those with one or two VRFs ($M = 2.80$, $SD = .76$) did not differ significantly from those with three or more VRFs, or those with no VRFs. Similarly, a significant negative (partial) correlation was found between number of VRFs and d' ($r = -.23$, $p = .03$), while adjusting for age, gender, and education. However, an ANOVA of our secondary measure of sustained attention (RT variability) with the same covariates was not significant ($F(2, 87) = 2.11$, $p = .13$, $\eta_p^2 = .046$) and there was no association between the number of VRFs and RT variability (CV; $r = .16$, $p = .13$) after adjusting for age, gender, and education. This suggests an additive and linear relationship between the number of VRFs and poorer sustained attention ability, as measured by performance accuracy (d').

Differences in Sustained Attention Based on Individual Risk Factors

We then investigated sustained attention differences across individual VRFs. ANOVA tests of our primary measure (d') were conducted across five VRF classifications using Bonferroni adjusted α levels of .01 per test (for the five VRFs). We observed lower d' in those with elevated blood pressure ($F(1, 88) = 4.90$, $p = .03$, $\eta_p^2 = .053$; Figure 2), elevated blood glucose ($F(1, 88) = 4.34$, $p = .04$, $\eta_p^2 = .047$; Figure 2), and elevated waist circumference ($F(1, 88) = 3.88$, $p = .052$, $\eta_p^2 = .042$; Figure 2), but these effects did not survive Bonferroni correction. We did not find significant d' differences based on classification for triglycerides ($p > .35$) or cholesterol ($p > .53$). Comparisons for our secondary measure of sustained attention ability (CV) were not significant based on any VRF classification. To explore the issue of overlapping groups within our sample, we conducted a multiple regression predicting d' with risk factor classifications of blood pressure, glucose, and waist circumference as predictors along with age, gender, and education. The model was not significant, $F(6, 86) = 2.18$, $p = .052$, with an R^2 of .072. Furthermore, none of the VRFs

Table 1
Sample Demographic and Vascular Health Information as a Function of Number of Flagged VRFs

	Means (*SD*)			Significance (ANOVA)
Sample size	0 ($n = 26$)	1 to 2 ($n = 35$)	3+ ($n = 32$)	Age range (years) (45–75)
Age (years)	61.94 (9.50)	59.34 (9.76)	65.28 (8.85)	$F(2, 90) = 3.56$, $p = .03$
Education (years)	17.12 (2.30)	16.20 (2.72)	15.69 (2.63)	$F(2, 90) = 2.22$, $p = .11$
Male (%)	57.8	68.6	78.1	$F(2, 90) = 1.39$, $p = .25$
Waist-hip ratio (cm/cm)	.85 (.08)	.94 (.08)	1.0 (.01)	$F(2, 90) = 21.3$, $p < .001$
Systolic blood pressure (mmHg)	111.04 (10.99)	133.17 (14.45)	132.28 (15.53)	$F(2, 90) = 22.6$, $p < .001$
Diastolic blood pressure (mmHg)	68.65 (9.78)	79.77 (8.48)	75.94 (7.87)	$F(2, 90) = 12.4$, $p < .001$
Fasting glucose (mg/dL)	88.19 (7.17)	93.89 (7.80)	112.97 (37.98)	$F(2, 90) = 8.84$, $p < .001$
Triglycerides (mg/dL)	73.5 (24.11)	103.97 (44.07)	121.69 (50.09)	$F(2, 90) = 9.56$, $p < .001$
HDL cholesterol (mg/dL)	66.65 (15.32)	55.11 (14.38)	48.38 (15.30)	$F(2, 90) = 10.8$, $p < .001$
Depression (BDI)	5.88 (5.57)	5.43 (6.53)	7.09 (7.25)	$F(2, 89) = .565$, $p = .57$

Note. VRFs = vascular risk factors; ANOVA = analysis of variance; HDL = high density lipid; BDI = Beck Depression Inventory. Means (*SD*).

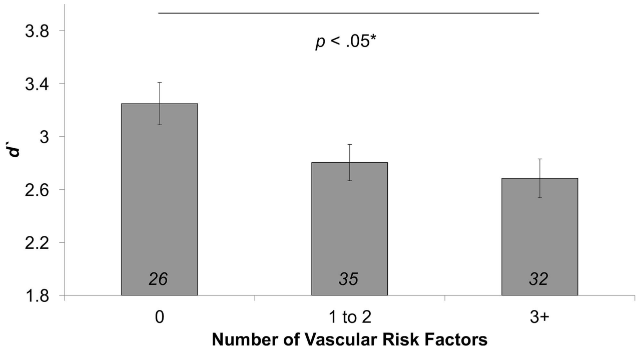

Figure 1. Significant effect of vascular risk group in which those with greater vascular risk displayed poorer discrimination ability. Marginal means of discrimination ability (d') across participants based on the number of vascular risk factors (VRFs) adjusted for age, gender, and education; 3+ denotes criteria for metabolic syndrome. Sample number is reported at the base of each respective bar.

alone uniquely predicted d' in the multiple regression (blood pressure ($\beta = -.146$, $p = .22$), glucose ($\beta = -.127$, $p = .27$), waist circumference ($\beta = -.11$, $p = .33$). This suggests that differences in d' across vascular risk groups most likely are explained by cumulative burden of VRFs in MetS, rather than a specific VRF uniquely driving the effect.

Neuropsychological Tests

No significant differences were found across vascular risk groups on the neuropsychological measures of executive function after adjusting for age, gender and education (assessing working memory, inhibitory control, and task switching; ref. Table 2; Figure 3). Furthermore, no linear relationships between number VRFs and scores for working memory ($r = -.11$, $p = .29$), inhibitory control ($r = .07$, $p = .51$), and task switching ($r = .09$, $p = .39$) were observed after adjusting for age, gender, and education. These results indicate that the gradCPT is more sensitive to the correlates of multiple VRFs on cognition than these traditional neuropsychological measures, despite these measures moderately correlating with d' (working memory $r = .37$, $p < .001$; task switching $r = -.47$, $p < .001$; inhibitory control $r = -.43$, $p < .001$).

Discussion

Our results demonstrate a relationship between sustained attention ability and the presence of multiple VRFs in a sample of middle-to-older aged adults. Specifically, healthy adults with lower vascular risk showed significantly better ability to sustain accurate performance on the gradCPT than participants with MetS, and with individuals who do not meet full criteria for MetS but have an intermediate level of risk. Further, an increase in the number of VRFs was linearly associated with worse performance across individuals. We did not find differences between groups on the neuropsychological tests of executive function (working memory, inhibitory control, and task switching); nor did we find such associations between neuropsychological tests and individual VRFs.

Sustained attention deficits have been reported across a wide variety of neurological and psychiatric patient populations, including developmental disorders (attention-deficit hyperactivity disorder [ADHD], autism), acquired brain injury (hemispatial neglect, traumatic brain injury), neurodegenerative diseases (Parkinson's, Alzheimer's, multiple sclerosis, and age-related cognitive decline) and psychiatric disorders (depression, posttraumatic stress disor-

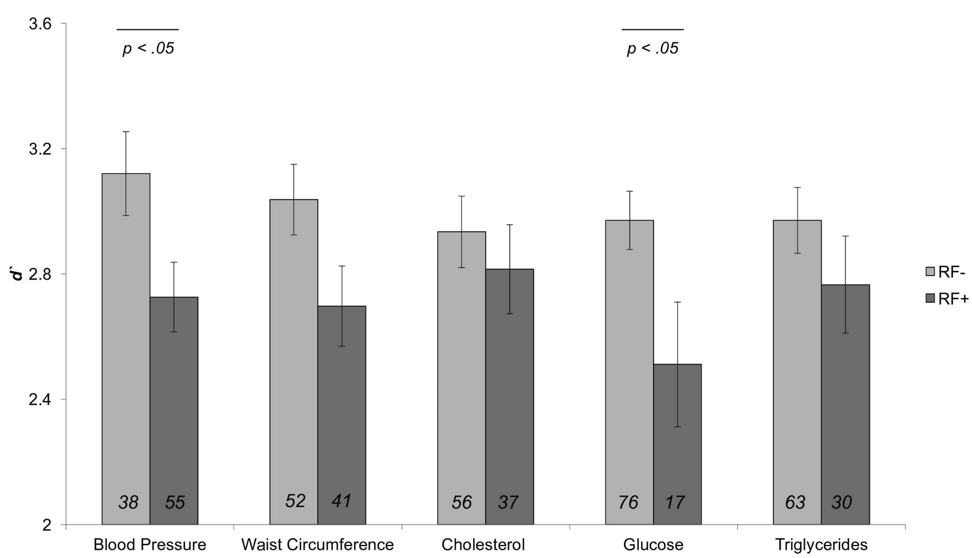

Figure 2. No difference in sustained attention ability based on individual vascular risk factor (VRF) classification after Bonferroni correction. Marginal means of discrimination ability (d') across participants based on classification of each individual VRF of metabolic syndrome adjusted for age, gender, and education. Sample number is reported at the base of each respective bar. RF− = did not meet criteria for VRF; RF+ = met criteria for VRF.

Table 2
Raw Means (SDs) of Neuropsychology Tests as a Function of Group

Components of sustained attention and EF	0	2 or 3	3+	Significance (ANCOVA)
GradCPT (Discrimination Ability (d'))	3.27 (.70)	2.80 (.76)	2.68 (.91)	$F(2, 87) = 3.60, p = .03, \eta_p^2 = .076$
GradCPT (RT Variability (CV))	.195 (.05)	.219 (.05)	.22 (.05)	$F(2, 87) = 2.11, p = .13, \eta_p^2 = .046$
Working memory	8.69 (1.96)	8.57 (1.80)	8.51 (2.00)	$F(2, 87) = .77, p = .47, \eta_p^2 = .017$
Inhibitory control	59.15 (18.47)	61.51 (18.48)	65.81 (15.83)	$F(2, 87) = .40, p = .67, \eta_p^2 = .009$
Task switching	86.84 (35.58)	107.89 (57.84)	109.78 (63.57)	$F(2, 86) = .72, p = .49, \eta_p^2 = .017$

Note. RT = reaction time; CV = coefficient of variation; EF = executive functioning. Analysis of covariance (ANCOVA) includes age, gender, and education as covariates. Executive Function (EF) Test: Working Memory = Digit Span Sequencing total (raw score); Inhibitory Control = D-KEFS Color Word Interference: Inhibition (total time); Task Switching = D-KEFS Trails: Number/Letter Switching (total time).

der, and bipolar disorder; Fortenbaugh et al., 2017). This, alongside neuroimaging studies, suggest that sustained attention can be impacted by compromise to a wide range of brain pathways and networks. Previous work has shown the gradCPT is sensitive to sustained attention deficits in several of these patient populations (depression and posttraumatic stress disorder; DeGutis et al., 2015), ADHD (Rosenberg et al., 2016), aging (Fortenbaugh et al., 2015), but has yet to be explored in adults with vascular risk and MetS (Fortenbaugh et al., 2017). MetS is characterized by the presence of at least three VRFs that each may have independent and differentiating neural effects when elevated beyond a healthy range (Leritz, McGlinchey, Kellison, Rudolph, & Milberg, 2011). The heterogeneous and subtle effects of vascular dysfunction may make it difficult to detect cognitive deficits in more modular domains, but rather may lead to more consistent impairments in sustained attention, which relies on broad coordination of multiple brain networks (Leritz et al., 2011). This may partly explain why groups did not differ on standardized measures of neuropsychological function, but differed on a sensitive measure of sustained attention (Fortenbaugh et al., 2018). Neuropsychological tests are often limited in their sensitivity to a cognitive deficit, particularly when examining specific aspects of a domain such as attention and executive function (Chan, Shum, Toulopoulou, & Chen, 2008; Esterman et al., 2018; Wasserman & Wasserman, 2012).

Despite the subtle nature of this deficit in sustained attention, this impairment could have clinical significance. Sustained attention can be considered a critical component of executive function, or the ability to maintain executive control over time. This ability serves a foundational role in an array of higher-level cognitive processes such as learning and memory, as well as other components of executive functioning such as inhibitory control and working memory (Fortenbaugh et al., 2017). While we did not detect impairments on traditional executive function measures, these subtle deficits may be a precursor to more widespread cognitive dysfunction, and highlight the importance of close monitoring of individuals with multiple VRFs, especially given the elevated risk for development of cognitive decline and dementia. Early detection of subtle vascular-related cognitive dysfunction presents a unique opportunity for preventative intervention to avoid progression to vascular related cognitive impairment and VaD.

Our findings are supported by prior neuroimaging studies demonstrating altered structural and functional integrity in individuals with higher vascular risk. Recently, our lab linked brain alterations in frontal regions in both white and gray matter to VRFs (Leritz et al., 2010; Leritz et al., 2011; Williams et al., 2013). More recently, we found reduced cortical thickness (CT) in frontal and temporal regions in MetS (Schwarz et al., 2018). Along with differences in CT, previous research has found microstructural white matter deficits in frontal and temporal regions to be associated with MetS (Segura et al., 2009). MetS has also been linked to increased prevalence of macroscopic damage, in the form of silent brain infarcts, periventricular hyperintensities, and subcortical white matter lesions (Bokura, Yamaguchi, Iijima, Nagai, & Oguro,

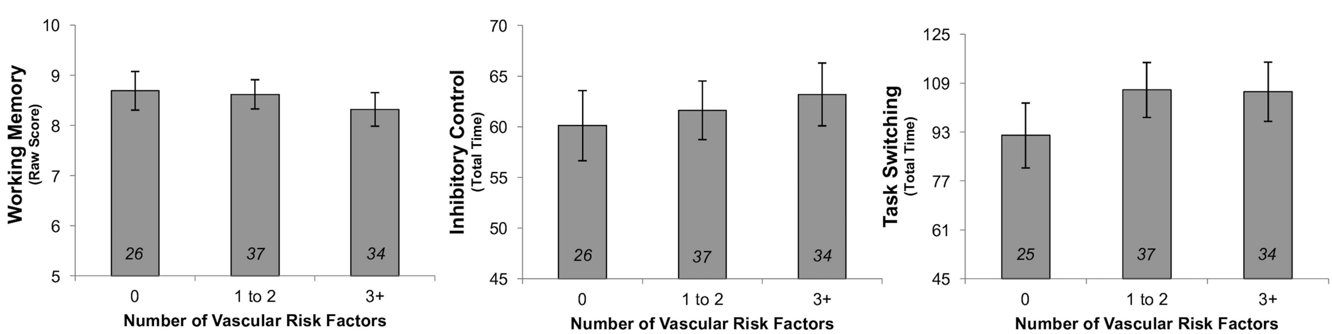

Figure 3. No differences in performance on working memory, inhibitory control, or task switching across participants based on number of vascular risk factors (VRFs) after adjusting for age, gender, and education; 3+ denotes criteria for metabolic syndrome. Sample number is reported at the base of each respective bar. Executive function domains and tests. Working Memory = Digit Span Sequencing total (raw score); Inhibitory Control = D-KEFS Color Word Interference: Inhibition (total time); Task Switching = D-KEFS Trails: Number/Letter Switching (total time).

2008). These types of macroscopic white matter damage have a strong association to executive dysfunction and cognitive decline (Yin et al., 2014). This is the case especially in early or predisease states, where white matter damage tends to be found in subcortical and periventricular regions likely important for attention and executive function (Van Den Heuvel et al., 2006). Thus, structural imaging findings support the idea that VRFs, especially when co-occurring as in MetS, are associated with loss of neural integrity in brain regions that are known to support sustained attention and executive function.

fMRI evidence is also consistent with our results. Previous work has found functional integrity to be altered in participants with MetS. Hoth and colleagues (2011) found participants who met metabolic criteria displayed lower BOLD response in the frontal-parietal control regions during a two-back verbal working memory task. Thus, the observed functional and structural alterations in MetS span many of the networks crucial for sustained attention, such as ECN, DAN, VAN, salience network, and DMN (Fortenbaugh et al., 2017). Using fMRI, our lab has established that these networks predict performance during sustained attention (Esterman et al., 2013; Fortenbaugh et al., 2018; Poole et al., 2016). In summary, the degenerative neural impact of MetS overlaps with regions critical for sustained attention.

Reduced attentional ability in MetS may be explained by a number of potential mechanistic factors. Peripheral inflammation may play an important role considering inflammation is a well-known risk factor for developing diabetes and atherosclerosis, and is often associated with vascular risk and metabolic syndrome (Dandona, Aljada, Chaudhuri, Mohanty, & Garg, 2005), as well as cognitive decline (Yaffe et al., 2004). Researchers have found declines in executive functioning associated with MetS to be significantly mediated by inflammatory biomarkers, such as c-reactive protein, proinflammatory and anti-inflammatory cytokines (Dik et al., 2007; Yaffe et al., 2004). Another possible mediator in the relationship between vascular health and sustained attention is physical activity. Physical activity can potentially play a major role in modifying and reducing vascular risk (Kim et al., 2011), and is an important factor to consider in future intervention or prevention studies.

Nonvascular risk factors are important confounders when considering our findings regarding MetS, and the absence of assessment of lifestyle factors such as smoking and sedentary behaviors, psychosocial stressors, and neuropsychiatric characteristics is a limitation of the current study. These factors play a major role in vascular disease progression as well. Psychosocial stressors such as bereavement, trauma exposure, social isolation, and marital stress; have been found to increase risk of cardiovascular disease and mortality (Everson-Rose & Lewis, 2005). Additionally, our sample size ($n = 93$) was relatively small to study subtle cognitive effects. Further, to contrast the gradCPT, we did not have comparable cognitive tasks in the protocol to surmise if the effects we have shown are unique to sustained attention, or if other such tests from different cognitive subdomains could reveal significant associations with vascular risk. Finally, the cross-sectional design of our study does not allow casual inferences of vascular risk on sustained attention. Prospective cohort studies designed to investigate longitudinal changes in sustained attention over time would be ideal to evaluate the association of progressive vascular dysfunction on sustained attention and executive functioning over time.

Despite these limitations, this work contributes to previous work on cognitive differences between healthy adults and adults with multiple VRFs by introducing novel differences in sustained attention ability, a foundational aspect of executive function. Our findings suggest that impairments in sustained attention are another facet to consider in the growing body of neurocognitive impairments associated with MetS and VRFs. Because of the strong relationship to MetS and underlying vascular impairments, sustained attention may be an early behavioral marker of vascular-related cognitive deficits. Our data support the fact that this may be the case even in individuals with one or two VRF elevations, who do not yet meet full MetS criteria. Thus, the gradCPT could be a useful tool to assess progression of neurocognitive dysfunction in relation to vascular health. Given the fact that sustained attention and executive function deficits are often correlated with everyday tasks such as paying bills or driving (Prouteau et al., 2004; Yanko & Spalek, 2013), identifying these impairments early when they are more subtle can be critically important for planning treatment and intervention strategies before the consequences become disabling. The gradCPT may also be effective in tracking the efficacy of interventions aimed at treating MetS-related executive dysfunction. Furthermore, neuroimaging could be useful in further understanding the structural and functional brain changes that may mediate the relationship between MetS and impaired sustained attention. Overall, these finding help contribute to understanding the complex relationship between cognition, vascular health, and MetS.

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