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What metabolic syndrome contributes to brain outcomes in African American & Caucasian cohorts

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Abstract

Metabolic syndrome (MetS), i.e., meeting criteria for any three of the following: hyperglycemia, hypertension, hypertriglyceridemia, low high-density lipoprotein and/or abdominal obesity, is associated with negative health outcomes. For example, MetS negatively impacts cognition; however, less is known about incremental MetS risk, i.e., meeting 1 or 2 as opposed to 3 or more criteria. We hypothesized incremental MetS risk would negatively contribute to cognition and relevant neuroanatomy, e.g., memory and hippocampal volumes, and that this risk extends to affective functioning. 119 non-demented/non-depressed participants (age=60.1±12.9; ~50% African American) grouped by incremental MetS risk–no (0 criteria met), low (1–2 criteria met), or high (3+ criteria met)–were compared across cognition, affect and relevant neuroanatomy using multivariable linear regressions. Exploratory analyses, stratified by race, consider the role of health disparities in disease severity of individual MetS component (e.g., actual blood pressure readings) on significant results from primary analyses. Incremental MetS risk contributed to depressive symptomatology (no<low<high), learning and memory performance (no>low=high) after controlling for age, race (n.s.) and IQ. Different indices of disease severity contributed to different aspects of brain structure and function by race providing empirical support for future studies of the impact distinct health disparities in vascular risk have on brain aging. MetS compromised mood, cognition and hippocampal structure with incremental risk applying to some but not all of these outcomes. Care providers may wish to monitor a broader spectrum of risk including components of MetS like blood pressure and cholesterol levels when considering brain-behavior relationships in adults from diverse populations.

Keywords

affect; aging; cognition; health disparities; metabolic syndrome; neuroanatomy; vascular risk

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Conflict of Interest

There are no actual or potential conflicts of interest.

1. INTRODUCTION

Vascular risk factors like hypertension and diabetes likely contribute to Alzheimer's disease (AD) either through non-amyloid related neuropathology and/or via a cascade of events that ultimately leads to amyloid-related alterations [1]. Regardless of mechanism, the negative contribution from vascular risk factors on brain aging lowers the threshold for developing AD [2–4]. When considered within the context of significant declines in US mortality rates from cardiovascular disease (CVD) and stroke [5], it appears older adults with CVD and associated vascular risks are living longer but they are not necessarily living well. This is particularly true in the African American (AA) population. Notably, AAs are over twice as likely to have diabetes (OR=2.58) and almost twice as likely to have high blood pressure (OR=1.88) when compared to CAs [6]. Additionally, AAs have significantly higher rates of uncontrolled vascular risk (58% versus 47%) than Caucasian Americans (CAs), regardless of socioeconomic status [7] or weight [8] - rates that are not declining despite declines in other populations [8]. Thus, at least half of the US population is at risk for increased vascular-related neuropathology leading to cognitive decline and dementia including AD [9]. Although AAs are disproportionately affected by elevated and often uncontrolled vascular risk, particularly diabetes and hypertension, and its negative impact on cognition and brain aging, less is known about how such risk manifests within the context of other vascular comorbidities. Gaining additional knowledge about coexisting disease states on brain aging may facilitate living well, not just living longer with CVD and associated vascular risk.

Investigating comorbid vascular risk as it relates to brain aging using known symptom clusters that are linked to CVD and associated vascular risks like hypertension and diabetes may highlight clinical profiles to monitor and individual symptoms to remediate both within and across populations disproportionately affected by these age-related disease states. Individuals with three or more of the following cluster of symptoms, including HTN, and hyperglycemia as well as hypertriglyceridemia, low high-density lipoprotein (HDL) levels and/or abdominal obesity are known to have Metabolic Syndrome (MetS) [10]. [10]The broad spectrum provided by symptom clustering in MetS and/or disease severity of individual MetS components (e.g., actual blood pressure readings) may help determine targets to monitor and symptoms to manage in order to facilitate successful brain aging. Furthermore, exploring if and how health disparities between AA and CA populations (groups known to have different prevalence rates and adequate control of vascular risk factors) may impact these profiles could better individualize treatment monitoring and management.

Memory, executive function and attention/information processing deficits are often associated with individual vascular risk factors (e.g., [11]) and sometimes, but not always [12], observed in individuals meeting three or more criteria for MetS [13–15]. Equivocal results in MetS may be due, in part, to the fact that a limited number of MetS studies of cognition (e.g., [16]) ensure that their healthy control comparison group did not meet any (i.e., no) MetS criteria. This leaves in doubt whether meeting one or two but not three or more criteria for MetS has an impact on cognitive functioning [15]. Others debate the importance of meeting criteria for MetS [17] versus displaying significant disease severity

across individual component parts [18] when investigating cognitive impairment. Thus, incremental MetS risk may be as important to cognitive functioning as MetS and/or individual vascular diagnoses when investigating brain aging in affected individuals.

These issues extend beyond cognition to encompass affect, an understudied area, particularly for AA populations [19, 20]. For example, there is a large literature linking select vascular diagnosis like Type 2 diabetes with depression [21]. In contrast, some [22, 23], but not all [24] MetS studies suggests increasing depressive symptomatology in adults with MetS. This may be due, in part, to the fact that there may be a more selective relationship between depression and disease severity of individual MetS components, e.g., triglyceride levels, than between depression and MetS per se [25]. More work should be done investigating affective functioning as it relates to conflicting results suggesting MetS as well as individual MetS components may play a role in depressive symptomatology.

We will address these gaps in the literature by evaluating cognitive as well as depressive symptomatology as it relates to meeting an increasing number of MetS criteria. We will also explore the role that health disparities in individual component severity may play in these profiles across AA and CA cohorts. Thus, our primary study aim is to provide information on the impact of meeting increasing MetS criteria regardless of race. We hypothesize that incremental MetS risk as defined by increasing symptom clusters (0 versus 1–2 versus 3+) will contribute to decreases in memory and executive functioning such that individuals with 3+ MetS risk will perform worse than individuals with 1–2 MetS risk who will perform worse than individuals with no MetS risk. We further hypothesize that relevant neuroanatomical volumes (e.g., medial temporal regions known to contribute to memory performance) will show similar profiles of MetS involvement such that individuals with 3+ MetS risk will have the smallest volumes while individuals with 1–2 MetS risk will show intermediate volumes between the 3+ and 0 risk groups. We also hypothesize that this profile of incremental risk, i.e., 3+ greater than 1–2 greater than 0, will also be seen for levels of depressive symptomatology. Lastly, we will explore the impact of health disparities in individual MetS component severity on significant results from our primary study aim to provide hypothesis generating evidence regarding differential contributions of individual vascular risk factors affiliated with MetS for AA versus CA as it relates to brain structure and function.

2. MATERIALS AND METHODS

2.1 Participants

Data collection was part of a larger research program on depression and Type 2 diabetes at the University of Illinois at Chicago (UIC) approved by the UIC Institutional Review Board and conducted in accordance with the Declaration of Helsinki. Volunteers age 30 and older were recruited via community outreach and underwent a preliminary telephone screen. Exclusion criteria consisted of current or past history of any of the following: neurological disorder (i.e., dementia, stroke, seizure, etc.), head injury or loss of consciousness, an Axis I disorder (e.g., major depression, bipolar disorder), substance abuse or dependence, psychotropic medication use.

After passing the telephone screen, participants were scheduled for a more detailed screening for final inclusion/exclusion determination that included a Mini-Mental State Examination (MMSE) [26] and the Structured Clinical Interview for DSM-IV (SCID). A trained research assistant administered these measures and a board certified/eligible (AK/OA) psychiatrist completed the 17-item Hamilton Depression Rating Scale (HDRS) [27]. Raters were blind to telephone screen information. All subjects were native English speakers, had an MMSE≥24, an absence of psychiatric symptoms based on the SCID, and a HDRS≤8. Two individuals had an MMSE<26; results did not change after excluding them; therefore, they remained in the sample. It is important to note that our cut-off scores for depression and cognition were not taken from the same assessment tools used to derive variables of interest for the analyses outlined below. This, combined with the fact that the MMSE is a gross measure of overall cognitive functioning, decreased the likelihood that the distribution of our variables of interest were unduly truncated by excluding participants with evidence of frank depression or dementia.

The final sample included 119 individuals (65 women; ~50% AA) approximately 60 years old (mean=60.1±12.9; range=30–89) with roughly 15 years of education (mean=14.9±2.7), MMSE scores of 28.8±1.3 and HDRS scores below cut-off for significant depressive symptomatology (1.2±1.5).

2.2 Vascular Assessment and Metabolic Syndrome Risk Evaluation

Laboratory testing from non-fasting blood draws documented levels of health related variables (e.g., cholesterol and glucose levels). It should be noted that levels of triglycerides and HDL are minimally affected by normal food intake [28] and as predictive of cardiovascular risk as fasting blood draws [28, 29]. The blood draw also provided a measure of hemoglobin A1c (hA1c), an important indicator of average blood sugar control over the past 2–3 months that is less affected by normal food intake [30]. The Cumulative Illness Rating Scale (CIRS) quantified the state and severity of current and past medical disorders.

MetS risk was determined based on International Diabetes Federation (IDF) criteria [31] which is in line with National Cholesterol Education Program's Adult Treatment Panel III report [32] with the exception of the classification of central obesity [33] as outlined below. Participants were given a point for every criterion met for blood pressure≥130/85mm/Hg, glucose≥100mg/dL, triglyceride≥150mg/dL, HDL cholesterol<40mg/dL (men) or <50mg/dL (women), and body mass index (BMI) >30 kg/m^2. Although IDF criteria focus on central obesity, these criteria also state that if BMI is greater than 30 kg/m^2, central obesity is presumed [31]. Medication was not considered in determining the number of MetS criteria met and discussed further in the limitations section of this manuscript. Additionally, IDF criteria allows for a diagnosis of Type 2 diabetes to count toward MetS totals in the absence of elevated glucose; however, we relied on glucose levels as opposed to diagnosis given some diabetics may be unduly penalized despite adequate control of their blood sugar. These instances were expected to be low given that approximately half of all AAs (58%) and CAs (47%) have uncontrolled vascular risk [7, 8] contributing a point toward MetS regardless. Supplemental tables provided as part of this submission show that

even when including a diagnosis of diabetes as a criterion toward MetS, our results profile remained the same (see Supplemental Materials online).

The total number of MetS criteria met was categorized to reflect incremental risk: no risk=0 criteria met, low risk=1–2 criteria met, and high risk=3 or more (3+) criteria met. We re-grouped individuals based on non-fasting glucose or 'random' blood draw cut-offs for glucose (≥200mg/dL) – the American Diabetes Association recommended cut-off for a diagnosis of diabetes and the cut-off for non-fasting blood draws used in previous MetS studies [34] – to ensure that our non-fasting measures of glucose did not unduly bias our results; as noted in the results below, they did not.

2.3 Neuropsychological and Neuroimaging Procedures

2.3.1 Neuropsychological Assessment—The neuropsychological assessment was conducted by a trained research assistant blind to MetS group and included a subjective measure of depressive symtomatology, the Center for Epidemiological Study of Depression scale (CESD) [35]. It also included standardized measures of predicted verbal intelligence (pVIQ; Wechsler Test of Adult Reading) and composite measures of Learning (LRN), Memory (MEM), Recognition Memory (REC), Attention/Information Processing (AIP) and executive functioning (EF). LRN comprised total recall for Trials 1–5 of the California Verbal Learning Test-II (CVLT-II) [36] and immediate free recall from the Wechsler Memory Scale-III (WMS-III; Logical Memory-I and Visual Reproduction-I) [37]. MEM consisted of CVLT-II long delay free recall and WMS-III delay free recall (Logical Memory-II and Visual Reproduction-II). REC consisted of recognition memory for Logical Memory and Visual Reproduction as well as a discriminability index from the CVLT-II [i.e., 1−(false positive errors+misses)/48)*100; max=100)]. AIP comprised the Stroop Color and Word raw scores, Trail Making Test (TMT) Part A time-to-completion and Wechsler Adult Intelligence Scale-III (WAIS-III) Digit-Symbol Coding raw score [38]. EF consisted of Category Switching total accuracy from the Delis-Kaplan Executive Function System batter [39], TMT-B time-to-completion, Stroop Interference Score, WAIS-III [38] Digit Span Backwards raw score and Self-Ordered Pointing Task total errors [40].

Raw scores were transformed to z-scores, coded so high scores reflected good performance then averaged to produce a mean score for each cognitive domain. Cronbach's alpha determined how well variables measured each latent construct; all values were considered good indicators of unidimensional latent constructs (α: LRN=.79; MEM=.75; REC= .63; AIP=.82; EF=.73).

2.3.2 Neuroimaging Data Acquisition—Whole brain MRI were acquired using Philips Achieva 3.0T scanner (Philips Medical Systems, the Netherlands) with an 8-element sensitivity encoding head-coil. Participants were positioned comfortably in the scanner, fitted with earplugs and instructed to remain still throughout the scan. Pads minimized head motion. High-resolution three-dimensional axial T1-weighted images were acquired with MPRAGE (FOV=240mm; contiguous slices=134; TR/TE=8.4/3.9ms; flip angle=8°; voxel size=1.1×1.1×1.1mm).

Forty-six participants did not have imaging leaving 84 with T1-weighted imaging. Reasons for missing data included claustrophobia(n=12); BMI(n=3); metallic implants(n=3); study withdrawal(n=3); lost to follow-up(n=1); repeat cancellations(n=3); data not acquired(n=9), lost(n=5), unavailable(n=3) or poor quality(n=1); (3=unknown). Characteristics and MetS groupings of this smaller sample remained unchanged from those reported for the larger sample. Compared to the 46 individuals without MRI, participants with MRI were older (61.4±12.2 versus 56.9±13.8; p=.054) and had higher pVIQs (106.3±14.1 versus 100.8±12.1; p=.03).

2.3.3 Neuroimaging Data Processing—Results were analyzed on an independent workstation (VMware, http://www.vmware.com/; Ubuntu platform, http://www.ubuntu.com/). It should be noted that prior to inclusion in this study, all scans were examined for space occupying and other focal lesions, including stroke. Eight potential participants were excluded from consideration; however, all subjects included in our analyses were free of any gross abnormalities. T1-weighted images were used to generate label maps using FreeSurfer for volumetric segmentation [41]. For this study, specific regions of interest (ROIs) within temporal and prefrontal cortices were calculated (right + left hemisphere) controlling for intracranial volume. Temporal ROIs included the hippocampus, entorhinal cortex, parahippocampal gyrus, and fusiform gyrus. Prefrontal ROIs included the superior, middle, and inferior prefrontal cortices and the orbitofrontal cortex. These ROIs were chosen given their known importance to memory and/or executive functioning [40, 42–44].

2.4 Statistical Analyses

Demographics were evaluated using analysis of variance (ANOVA) for continuous variables and chi-square for categorical variables. We used multivariable linear regression analysis to examine the association of increasing MetS criteria (no, low, and high) with depressive symptomatology, cognitive functioning, and relevant neuroanatomy as dictated by results of the cognitive analyses. All analyses were adjusted for age, race, and IQ. For cognitive outcomes, we also controlled for depressive symptomatology given its association with CVD as well as cognition [45, 46]. Given sex differences in brain morphometry [47], sex was an additional covariate for neuroanatomical outcomes. Given we were testing pre-specified hypotheses, we did not correct for multiple comparisons in our analyses. Furthermore, correcting for multiple exposures would have decreased our power to detect true associations and increase the false negative rate [48].

As warranted by the results of our first set of analyses, a second set of regression modeling was conducted to investigate the impact of individual MetS component disease severity (i.e., glucose, HDL, and triglyceride levels; blood pressure; BMI) on behavioral and relevant neuroanatomical outcomes significant for the entire group stratified by race to explore if the differential profiles of vascular risk known to exist for CAs and AAs also exerted their influence on associated behavioral and/or neuroanatomical profiles. We also considered hA1c in our severity analyses, given it provides more long-term information regarding control of blood sugar and diabetes. Severity metrics were only considered in the models if they were found to be significantly correlated with the outcome of interest at $p<0.05$.

Forward and backward selection procedures (performed manually) were used to determine the best-fitting and most parsimonious models. Analyses were performed using SASv9.4 (SAS Institute Inc, Cary, NC).

3. RESULTS

Groups differed by age [F(2,118)=3.4, p=.04] and pVIQ [F(2,118)=5.6, p=.005]. Thus, individuals at no MetS risk, i.e., meeting 0 criteria, were younger than any other group (no<low=high; p's≤.04) and individuals meeting 0, 1 or 2 MetS criteria had higher pVIQ than individuals meeting 3+ MetS criteria (no=low>high; p's≤.01). There were no significant differences on any other demographic variables (Table 1).

As previously stated, our sample was taken from a larger study of individuals with and without Type 2 diabetes. The percentage of our sample with Type 2 diabetes (men=20%; women=21%) was commensurate with percentages reported for the State of Illinois (23.8%) [49]. As expected, however, the presence and duration of diabetes was significantly different between MetS groups (p-values<0.001). Individuals in the high risk or 3+ MetS group showed the highest levels of diabetes (80% of the 3+ group had diabetes) and for the longest duration (Table 1) compared to individuals in the low or no risk categories. Furthermore, hA1c levels were significantly different [F(2,118)=19.6, p<.001] such that individuals meeting 3+ criteria showed the highest levels followed by individuals meeting 1–2 criteria followed by individuals meeting no criteria (i.e., high>low>no; p-values≤0.05). Overall illness burden as measured by the CIRS was significantly different between groups [F(2,118)=159.3, p<0.001] such that increasing MetS criteria equated to increasing CIRS (no<low<high; p-values≤0.003).

3.1 COGNITIVE DOMAINS

As hypothesized, incremental risk based on meeting an increasing number of MetS criteria was significantly associated with LRN and MEM, with marginal trends seen for EF (Table 2). There were no significant results for AIP or REC. Unlike our hypothesis, however, individuals at no risk outperformed individuals at either low (1–2 MetS criteria met) or high (3+ MetS criteria met) risk across LRN and MEM. When we used non-fasting glucose cut-off criteria to create MetS criteria groups, results were similar.

3.2 NEUROANATOMY

Despite significant correlations between our temporal ROIs and LRN and MEM composite z-scores – with the exception of the entorhinal cortex (Table 3), increasing MetS criteria did not contribute to structural volumes associated with our significant learning and memory findings, i.e., hippocampal, parahippocampal, entorhinal and fusiform volumes. When we used non-fasting glucose cut-off criteria to create MetS groups to ensure that our non-fasting measures of glucose did not unduly bias our results (Results Section 2.2), results revealed that increasing MetS criteria did contribute to hippocampal volumes. Thus, individuals meeting 1–2 MetS criteria had smaller hippocampal volumes (B=−0.0007, SE=0.0003, p=0.04) than individuals meeting no MetS criteria. Individuals meeting 3+ MetS criteria had smaller hippocampal volumes than individuals meeting no MetS criteria; however, this

result was not significant p=0.07. Given that fasting/non-fasting cut-off criteria resulted in discrepant results, we did not conduct exploratory analyses stratified by race.

3.3 DEPRESSIVE SYMPTOMATOLOGY

As hypothesized, incremental risk groupings were a significant predictor of depressive symptomatology (Table 2). Controlling for pVIQ, age and race (not a significant covariate in this model), individuals at high risk, i.e., meeting 3+ MetS criteria, reported more depressive symptoms than individuals with low (1–2 MetS criteria met) or no risk. Individuals meeting 1–2 MetS criteria reported more depressive symptoms than individuals at no risk after adjustment for pVIQ, age and race; however, this result was not significant p=0.08. When we used non-fasting glucose cut-off criteria to create MetS criteria groups, results were similar.

3.4 EXPLORATORY ANALYSES STRATIFIED BY RACE

When we stratified our sample by race, increasing diastolic blood pressure significantly contributed to both LRN (B=−0.01, SE=0.07, p=0.089) and MEM (B=−0.01, SE=0.001, p=0.04) in the CA cohort; increasing triglyceride levels (B=−0.002, SE=0.001, p=0.056) also contributed to MEM scores in the CA cohort. In contrast, results revealed the importance of elevated glucose (B=−0.003, SE=0.01, p=0.009) on LRN and increasing systolic blood pressure on MEM (B=−0.01, SE=0.048, p=0.001) within the AA cohort.

When we stratified our sample by race, results revealed the importance of increasing hA1c (B=2.19, SE=0.75, p=0.004) and triglyceride levels (B=0.02, SE=0.008, p=0.003) to CESD scores in the CA group. There were no significant contributes to CESD scores within the AA cohort as it related to MetS component disease severity.

4. DISCUSSION

As hypothesized, the presence of metabolic risk factors compromised memory and related hippocampal structures as well as mood when compared to the absence of metabolic risk factors. Apart from increasing MetS criteria being associated with increasing depressive symptoms, meeting 3 or more MetS criteria did not distinguish between alterations in cognitive functioning seen when only 1–2 MetS criteria were met. In fact, the neuropsychological profile associated with meeting only 1–2 MetS criteria, may be as detrimental as the high risk category. More specifically, results consistently revealed alterations in learning and memory on the order of a 0.5 standard deviation unit decrement in these cognition domains when individuals meeting 1–2 or 3 or more MetS criteria were compared to those meeting no (0) criteria. This suggests that the cognitive similarities of meeting 1–2 MetS criteria versus 3 or more may explain some of the null results reported in previous studies of MetS and cognition when the non-MetS comparison group consisted of individuals not meeting 3 or more criteria for MetS [50] as opposed to individuals not meeting any criteria for MetS [16]. These results may also suggest that i) once an individual meets a particular threshold of metabolic risk, there is a ‘plateau’ effect for select cognitive functions such that increasing risk factors no longer increase cognitive compromise and ii) this threshold may be as low as 1–2 vascular risk factors.

Our investigation of encoding (learning), retrieval (memory), and recognition suggests that it is the first two of these cognitive processes, i.e., encoding and retrieval that are negatively – and equally – impacted by any MetS risk in our cross-sectional study. Poor performance during spontaneous recall is often facilitated by recognition testing in individuals with vascular-related cognitive deficits regardless of dementia [51, 52]. Results in our sample of Caucasian and African Americans corroborate and extend this finding to a non-depressed, non-demented cohort of vasculopaths. Additionally, the fact that individuals meeting increasing MetS criteria showed smaller hippocampal volume than individuals meeting no MetS criteria but no differences in executive function tasks suggest that recognition memory may have been facilitated by intact prefrontal circuitry known to be associated with these cognitive functions regardless of race. Future studies incorporating more in-depth neuroimaging techniques are needed to adequately address our preliminary conclusions although there are some existing gross morphometric studies that support this assertion in other vascular, e.g., diabetic, populations [53, 54].

Results for learning, memory and hippocampal integrity from our primary analyses, speak to the negative role co-existing disease states may play on brain behavior relationships [55]. Vascular risk factors like hypertension, diabetes and dyslipidemia – facets of which contribute to MetS criteria – increase inflammation and decrease blood brain barrier integrity [56, 57]. Likewise, they make the brain more vulnerable to other pathologies, most notably white matter and amyloid-related alterations [58]. Using amyloid as an example, vascular risk factors directly lower blood flow thus diminishing a-beta peptide clearance from the CNS which in turn increases amyloid accumulation in brain. These general discussions of the vascular risk spectrum represented by MetS says nothing of the role insulin and the insulin signaling transporter system – key players in glucose levels and diabetes as well as dyslipidemia associated with MetS – play in hippocampal dysfunction both structurally and functionally [59]. Thus, our association between learning and memory and relevant neuroanatomy as well as the role of increasing MetS on hippocampal structural integrity suggests that more work needs to be done investigating comorbid vascular risk as it relates to brain aging using known symptom clusters that are linked to insulin and insulin resistance.

Our exploratory analyses of the specific contributions of individual MetS component's disease severity by race, revealed differential profiles of statistically significant disease predictors based on the behavior assessed. Thus, when stratified by race, distinct patterns of individual disease involvement selectively contributed to depressive symptoms as well as learning and memory. More specifically, for every unit increase in hA1c, CAs showed a 2.2 point increase in depressive symptomatology. While triglycerides also contributed to depressive symptomatology in this group, replicating previous work [25] the unit increase in the current study was marginal even when equated for meaningful change per measurement to hA1C; e.g., a 50 unit increase in triglyceride levels that equates to a move from borderline high (150 mg/dL) to high (200 mg/dL) only resulted in a 1 point increase in depressive symptomatology. No one individual disease contributed to depressive symptomatology in the AA group. In contrast, disease severity differentially contributed to learning and memory scores for Caucasian and African Americans. While the more long-term indicator of blood sugar control, hA1c, predicted affective functioning in CAs, the more short-term, daily

indicator of blood sugar control, glucose, predicted cognitive functioning in AAs. Additionally, diastolic blood pressure contributed to learning performance in the Caucasian group and also predicted memory performance in this same group along with levels of triglycerides. Only systolic blood pressure predicted memory performance in the AA group. It should be noted, however, that the standard deviation unit decrements associated with a unit change in any of these predictors from pre-clinical to diagnostic states (e.g, a 25 unit shift in glucose or a 10–20 unit shift in systolic or diastolic blood pressure) were small – less than one-fifth of a standard deviation. Thus, while these preliminary results revealed unique aspects of disease severity as contributors to learning and memory by race, the extent to which these specific aspects of MetS are driving these cognitive profiles is unclear and warrant further exploration in a larger sample.

Regardless of clinical impact, our exploratory analyses regarding disease severity of individual MetS components provide hypothesis generating evidence for future studies investigating how such things as glucose, blood pressure and triglycerides may be differentially influencing cognition by race. For example, we investigated systolic and diastolic pressure as distinct and continuous variables; as a result, the relationship between these metrics and brain function was not constant and may reflect different manifestations known to occur in diverse populations [60]. Thus, the differential influence systolic and diastolic blood pressure variables had on brain function by race, however minimal, may attenuate and/or cancel out when they are combined either within or across diverse populations. Differential involvement of indices associated with blood sugar control were also revealed when we stratified by race; i.e., long-term measures of control contributed to behavioral outcomes (depressive symptoms) in CAs while short-term measures of control contributed to cognitive outcomes (learning) in AAs. Although debate still exists on the presence of health disparities in hA1c levels [30], our result may reflect the functional impact of these possible differences [61]. Future studies emanating from these exploratory findings by race should focus on the role of minority health disparities in distinct blood pressure indices or distinct blood sugar metrics and/or their role in insulin resistance and the insulin network more broadly [59] on brain behavior relationships.

This study is not without limitations and by outlining them we hope they will point toward future research. Our sample was drawn from a larger study of diabetes. As such, our MetS groups differed in terms of their diagnosis, duration and control of diabetes, which resulted in a linear increase in these variables when moving from the no risk to the low risk to the high risk groups of our study. Despite this, we found non-linear associates to brain structure and function regardless of how we incorporated this particular MetS component as well as non-glucose related disease severity indices contributing to dysfunction when we stratified by race. Our investigation of relevant neuroanatomy revealed little and may have been negatively impacted by the gross volumetrics and/or select ROIs used in this study. An additional limitation of our work was that we did not divide our MetS groups by sex – primarily because of sample size limitations – however, considerations remain which are unique to women that may influence the number of MetS criteria met and/or disease severity of individual MetS components [62]. Likewise, investigating treatment regimens across MetS criteria groups, while critical to this work, requires a larger study than ours.

CONCLUSION

This study revealed a profile of increasing depressive symptomatology when meeting increasing MetS criteria and a profile of learning and memory impairment when meeting any MetS criteria. The impact of health disparities in vascular risk were explored by investigating the contributions of disease severity of individual MetS components to these profiles by race. For example, results suggested a possible differential role for long- versus short-term measures of blood sugar control on affect and cognition based on CA and AA groups that should be investigated more directly in future research. Little to no impact was observed in global measures of relevant neuroanatomy; however, more subtle metrics of brain structure may be warranted to detect an impact of MetS risk in this diverse population. Overall, it appears there is a low threshold of metabolic risk for cognitive compromise in our sample of Caucasian and African Americans. This suggests we must incorporate a broader spectrum of subclinical CVD indices beyond those addressing the state or severity of one particular disease if we are to determine appropriate targets for risk modification and successful brain aging in adults from diverse populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Metabolic Syndrome (MetS) Group Characteristics

	No Risk (0 MetS criteria) n=20	Low Risk (1–2 MetS criteria) n=60	High Risk (3+ MetS criteria) n=39
Group Characteristics			
Age (years)[a]	53.5±14.2	62.8±12.4	60.6±12.3
Education (years)	15.5±3.1	15.3±2.7	14.1±2.4
Sex (M:F)	6:14	31:29	17:22
Race (B:W)	6:14	30:30	21:18
pVIQ[b]	110.5±10.1	106.1±13.1	99.1±15.0
Diabetes Presence (%)	0%	31%	80%
Diabetes Duration (months)	n/a	29.3±57.9	72.2±72.6
CIRS[b]	2.2±2.1	5.0±3.2	7.0±3.5
Criterion Met (%)			
HDL	0	13	66
Glucose	0	36	66
HTN	0	66	77
Triglyceride	0	8	74
BMI	0	35	77

[a] $p<.05$;

[b] $p\leq.005$;

M:F=male:female; B:W=black:white;

pVIQ=predicted verbal IQ; CIRS=Cumulative Illness Rating Scale.

Table 2

Results of Multivariable Linear Regressions Examining the association of increasing MetS criteria on affect and cognition.

	Affect		Cognition‡	
Variables	**CES-D B (SE)**	**LRN B (SE)**	**MEM B (SE)**	**ExFx B (SE)**
African American (vs White)	1.02 (1.24)	−0.16 (0.18)	−0.27 (0.17)	−0.02 (0.14)
MetS Criteria Met				
1–2 vs 0	1.97 (1.12)^{T}	−0.39 (0.16)*	−0.48 (0.16)**	−0.24 (0.13)^{T}
3+ vs 0	4.73 (1.23)***	−0.42 (0.19)*	−0.50 (0.18)**	−0.12 (0.15)
3+ vs 1–2	2.75 (0.89)**	−0.03 (0.13)	−0.02 (0.13)	0.12 (0.10)

NOTE:

*** p<0.001;

** p<0.01;

* p<0.05;

^{T} p>0.05 and p≤0.10;

MetS=Metabolic Syndrome; 0=no risk, 1–2=low risk, 3+=high risk; CES-D=Center for Epidemiologic Studies of Depression; LRN=composite z-score for Learning; MEM=composite z-score for Memory; ExFx=composite z-score for Executive Functioning. All analyses are adjusted for age, race, and pVIQ.

‡ Cognitive outcomes were also adjusted for the CES-D.

Table 3

Correlations between significant results of cognitive analyses and relevant neuroanatomical regions of interest.

	Learning (LRN)	**Memory (MEM)**
Relevant Neuroanatomy		
Hippocampus	r(74)=.33, p=0.004	r(74)=.32, p=0.005
Entorhinal Cortex	~~r(74)=.17, p=0.148~~	~~r(74)=.21, p=0.064~~
Parahippocampal Gyrus	r(74)=.33, p=0.004	r(74)=.35 p=0.002
Fusiform	r(74)=.42, p<0.001	r(74)=.38, p=0.001

Note: All 2-tailed analyses are adjusted for age, sex, race, pVIQ as well as CES-D and met significance based on correction for multiple-comparisons ($p \leq 0.006$).