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BACKGROUND AND PURPOSE: MetS is a cluster of risk factors associated with significant cardiovascular morbidity and mortality and diminished cognitive function. Given that little is known about the early signs of brain vulnerability related to persistent metabolic dysfunction, we set out to determine whether cognitively healthy middle-aged individuals with MetS exhibit an altered cerebrovascular response to a cognitive challenge relative to those without MetS.

MATERIALS AND METHODS: Forty neurologically healthy adults aged 40–60 years (19 with MetS and 21 healthy controls) performed a 2-back verbal working memory task during fMRI. We compared BOLD responses between the 2 groups in 8 a priori regions of interest previously shown to be associated with the 2-back in patients with cardiovascular disease.

RESULTS: Age, education level, sex distribution, cognitive and emotional functioning, and task performance (accuracy and reaction time) were not different between the groups. Compared with healthy controls, individuals with MetS demonstrated a lower 2-back–related BOLD response in the right superior frontal gyrus, right superior parietal lobule, and left inferior parietal lobule.

CONCLUSIONS: This study provides preliminary evidence that cognitively intact middle-aged individuals with MetS exhibit significant alterations in cerebrovascular response to a cognitive challenge. Our results also demonstrate that fMRI may identify early brain changes associated with MetS.

ABBREVIATIONS: AD = Alzheimer disease; AFNI = Analysis of Functional NeuroImages; BMI = body mass index; BOLD = blood oxygen level–dependent; CVLT-II = California Verbal Learning Test-II; EPI = echo-planar imaging; fMRI = functional MR imaging; HDL cholesterol = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; IQ = intelligence quotient; LDL cholesterol = low-density lipoprotein cholesterol; MetS = metabolic syndrome; MMSE = Mini-Mental Status Examination; MS = multiple sclerosis; RCF = Rey Complex Figure Test; WASI = Wechsler Abbreviated Scale of Intelligence; WM = white matter

The number of elderly patients with dementia is expected to quadruple during the next 50 years.[1] In addition, a great number of older adults are projected to develop milder forms of cognitive impairment.[1] This trend is alarming because cognition is the most important determinant of health status, quality of life, and functional ability in older age.[2] Diminished cognitive capacity causes significant psychological, social, and economic hardship and adversely impacts a person's ability to benefit from treatment for other medical problems.[3] Due to the current paucity of treatments for dementia, management of treatable factors that place the brain at risk for subsequent cognitive decline is the primary line of defense, especially in cases in which vascular factors play a key role.[4-7]

MetS refers to a clustering of risk factors (ie, hypertension, hyperglycemia, dyslipidemia, and obesity) associated with increased cardiovascular morbidity and mortality.[8] Growing evidence suggests that MetS is also harmful to cognition and that the cluster may have predictive value for cognitive decline over and above that of its individual components.[9-16] Older patients with MetS score lower on cognitive tests than age-matched healthy adults, particularly on measures of processing speed and executive functioning,[17] cognitive domains that are associated with vascular cognitive impairment. Several studies have shown that middle-aged individuals with MetS are at higher risk of developing dementia in late life,[18] yet accurate prediction of individual cognitive trajectories is difficult due to the low sensitivity of paper-and-pencil screening tests to subtle changes in intellectual functioning. Neuroimaging studies have shown promise in identifying individuals at risk for subsequent cognitive decline because these studies revealed that MetS is associated with early alterations in the structural integrity of cerebral white matter.[19-21]

BOLD fMRI has the potential to contribute further to our understanding of early cerebrovascular changes related to persistent metabolic dysfunction. Alterations in the BOLD response to cognitive challenges have been shown in cognitively asymptomatic patients with MS, HIV infection, and genetic risk for AD.[22-27] BOLD fMRI performed during cognitive tasks, therefore, can help elucidate the complex relationship between metabolic and vascular health, cerebrovascular support for cognitive function, and behavioral performance. An accurate model of the relationship between cerebrovascular health and persistent metabolic dysfunction at midlife could prove instrumental in increasing the success of broader efforts to prevent and treat vascular cognitive impairment.

Table 1: Selected demographic and physiologic characteristics of subjects

	Controls (n = 21)	MetS (n = 19)	P Value
Male/female	9/12	13/6	.105
Age (yr)	50.4 ± 5.3	47.4 ± 6.0	.075
Education level (yr)	14.9 ± 2.0	15.5 ± 3.5	.675
Systolic blood pressure (mm Hg)	121 ± 12	135 ± 18	.010[a]
Diastolic blood pressure (mm Hg)	74 ± 7	81 ± 11	.046[a]
BMI (kg/m²)	26.9 ± 4.7	34.8 ± 4.1	<.001[a]
HDL cholesterol (mg/dL)	55.6 ± 14.5	39.1 ± 9.2	<.001[a]
Triglyceride (mg/dL)	124.5 ± 63.8	250.8 ± 98.8	<.00[a]
LDL cholesterol (mg/dL)	131.6 ± 39.3	127.3 ± 30.6	.922
Fasting glucose (mg/dL)	93.4 ± 6.8	133.8 ± 50.6	<.001[a]

[a] Significant.

To our knowledge, no studies have examined functional neuroimaging in MetS. Accordingly, the aim of this study was to test the hypothesis that middle-aged adults with MetS would show altered patterns of brain activation (ie, BOLD responses) during a verbal working memory task. The chosen task requires selective attention, executive ability, and psychomotor speed, cognitive abilities typically affected in vascular-related cognitive impairment. As such, they may have particular relevance for MetS.

Materials and Methods

Participants

Right-handed[28] participants between 40 and 60 years of age were recruited through flyers and newspaper advertisements. Participants were excluded if they had a history of neurologic disease (ie, large-vessel stroke, seizure disorder, Parkinson disease, clinically significant traumatic brain injury, MS, or brain infection/meningitis), major psychiatric illness (eg, schizophrenia, bipolar disorder), substance abuse (diagnosed abuse and/or previous hospitalization for substance abuse), or MR imaging contraindications. Forty individuals participated in the study. The mean age of those participants was 50.0 ± 6.0 years (range, 40–60 years; median age, 50 years). The mean education level was 15.2 ± 3.0 years. The mean full-scale IQ score was 115.0 ± 10.5, indicating high average global cognitive functioning according to published norms.[29] Enrollees identified themselves as follows: 43% white, 35% Hispanic, 8% African American, 5% Asian American, and 9% other/did not specify.

Procedures

The study was conducted in accordance with the Helsinki Declaration of 1975 with approval from the local institutional review board. All volunteers provided written informed consent before enrollment. Participants completed a medical history interview with a research assistant. Medical conditions and treatments were coded as either present or absent according to the participant self-report. Participants underwent a general health assessment, a full neuropsychological evaluation, and brain imaging on separate days, completing the study within 1 month.

General Health Assessment and MetS Classification. Fasting blood concentrations of glucose, triglycerides, HDL cholesterol, and LDL cholesterol were determined by using the standard enzymatic techniques. Arterial blood pressure was measured by using a standard oscillometric blood pressure monitor after at least 15 minutes of rest (VP-2000; Colin Medical Instruments, San Antonio, Texas). BMI was calculated as body weight in kilograms divided by the square of the height in meters. Prescription medications were coded as present or

absent according to the participant self-report and were classified as antihypertensive, lipid-lowering, hypoglycemic, antiplatelet, anti-inflammatory, antidepressant, antihistamine, hormone replacement, biphosphonates, or vitamins.

MetS was defined according to the 2009 criteria issued jointly by the International Diabetes Federation, National Heart, Lung, and Blood Institute, the American Heart Association, World Health Federation, International Atherosclerosis Society, and International Association for the Study of Obesity.[8] Participants were included in the MetS group if they fulfilled at least 3 of the flowing criteria: abdominal obesity (BMI of >30 kg/m², equivalent to waist circumference ≥94 cm for men and ≥80 cm for women[8]); elevated triglycerides (≥150 mg/dL) or treatment for elevated triglycerides; reduced HDL cholesterol (<40 mg/dL for men and <50 mg/dL for women) or treatment for reduced HDL cholesterol; elevated blood pressure (systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥85 mm Hg) or antihypertensive drug treatment; elevated fasting glucose (≥100 mg/dL) or treatment with a hypoglycemic agent. Participants were currently being treated in the following manner: 8 with antihypertensive medications, 2 with antiplatelet agents, 2 with lipid-lowering agents, 3 with hypoglycemics, 1 with thyroid replacement therapy, 2 with bisphosphonates, and 3 with antidepressant medication. Further details about the demographic and physiologic characteristics of the sample and comparisons between the control and metabolic syndrome groups can be found in Tables 1 and 2.

Neuropsychological Evaluation. All participants completed a 2-hour assessment battery, including standard clinical neuropsychological instruments with established reliability and validity.[30] The battery included measures of global cognitive functioning (MMSE[31]; WASI[29]), language (WASI Vocabulary subtest; Category Fluency for Animals[32]), memory (CVLT-II[33]; RCF[30]), attention-executive functioning (Digit Vigilance [34]; Controlled Oral Word Association Test[35]; Trail Making Test A and B[36]), psychomotor speed (Grooved Pegboard, Pegs[37]), visual-spatial ability (RCF copy; WASI Matrix Reasoning subtest), and emotional functioning (Beck Depression Inventory-II).[38] All tests were administered and scored by a trained research assistant by using standard administration and scoring criteria.

Neuroimaging. Each imaging session included working memory task practice, T1-weighted imaging for anatomic reference, and 2 imaging runs of the working memory task. The 2-back task was presented by using E-Prime software (Psychology Software Tools, Pittsburgh, Pennsylvania) back-projected onto a screen positioned at the participant's head and viewed through a double-mirror attached to the head coil. Responses were collected by using an MR imaging−compatible response box.

Table 2: Cognitive and emotional functioning

Cognitive Domain Sample-Based z Score	Controls (n = 21)	MetS (n = 19)	P Value
Global	0.14 ± 0.66	−0.18 ± 0.94	.228
Language	0.01 ± 0.92	0.03 ± 0.59	.962
Visual-spatial	−0.01 ± 0.63	0.01 ± 0.83	.912
Memory	−0.01 ± 0.64	−0.04 ± 0.92	.449
Attention-executive-psychomotor	0.07 ± 0.56	−0.09 ± 0.68	.427
Reported depressive symptoms	5.60 ± 4.30	7.00 ± 5.87	.728
2-Back accuracy (% correct)	83.46 (10.0)	76.0 (18.6)	.339
2-Back reaction time (ms)	1078.8 (280.9)	1207.2 (348.1)	.258

MR Imaging Data Acquisition. MR imaging data for each participant were acquired in a single session on a 3T Signa Excite MR imaging scanner (GE Healthcare, Milwaukee, Wisconsin) equipped with a standard head coil. Structural imaging included a high-resolution spoiled gradient-recalled (256 × 256 matrix, FOV = 24 × 24 cm^2, 1-mm section thickness, 0 gap) anatomic scan of the entire brain in the sagittal plane. Functional imaging was performed by using a whole-brain EPI sequence (TR = 3000 ms, TE = 30 ms, FOV = 24 × 24 cm^2, 64 × 64 matrix, 42 axial sections, 3-mm section thickness, 0.3-mm gap).

Working Memory Paradigm. Working memory was assessed by using a verbal 2-back task. During this task, a series of individual consonants was presented visually for 500 ms each with a 2500-ms interstimulus interval. Consonants were arranged in random order from a list of all consonants except "L" due to ambiguity in the lowercase form. For each stimulus, participants were asked to determine if the letter on the screen was the same as or different from a previously presented letter. Responses were collected by using a 2-button MR imaging–compatible response box. A 0-back control condition was alternated with the 2-back condition in a block design. Two imaging runs, each consisting of 3 blocks of the 0-back, 3 blocks of the 2-back, and 3 blocks of rest presented in alternating order and lasting approximately 6 minutes, were conducted.

0-Back Control Condition. This task consisted of 3 blocks of 12 consonants of random case and order, 33% of which were targets. Participants responded yes when the upper or lowercase letter *H* appeared on the screen or no if another letter appeared.

2-Back Working Memory Condition. The experimental condition consisted of 3 blocks, each containing 15 consonants of random case and order, 33% of which were targets. A letter was considered a target if it was the same as the letter presented 2 stimuli earlier regardless of the case (eg, s, G, *S*, d, V, *D*, *v*, and so forth). Task performance was assessed by measuring accuracy rates and mean reaction time for all correct trials.

Rest. The participants were instructed to rest for 30 seconds while focusing their attention on a fixation cross that appeared in the middle of the screen.

fMRI Data Processing. All EPI images were processed by using AFNI software (http://afni.nimh.nih.gov/afni/).[39] Each time-series was spatially registered to the sixth volume of the session to reduce the effects of head movement. This AFNI 3D registration program also yielded information on displacement and rotation for each volume, which was used later to further correct motion. All participants moved <1.5 mm per imaging run, and no participants were excluded from the analyses due to excessive head motion. Data preprocessing also included adjustment for differences in adjacent-section timing due to interleaved section acquisition, temporal smoothing, and spatial filtering. Task-related brain activation was determined by using within-subject voxelwise multiple regression analyses with the following parameters: a 0-back/2-back reference waveform convolved with a γ function and covariates accounting for instruction screens and head movement. Averaged task-related activation within a set of 8 a priori regions of interest was examined in subsequent analyses.

A separate dataset was used to create empirically defined task-related regions of interest for hypothesis testing to avoid circularity. The task used to create the regions of interest was identical to the one used in the current study. The sample and the creation of the regions of interest are described in detail in Haley et al.[40] Briefly, the regions of interest were created by transforming the results from individual multiple regression analyses to standard stereotaxic space[41] and converting them to z scores. The z scores were then thresholded at $P < .05$, corrected for multiple comparisons by using the false discovery rate supplied by AFNI. Voxels were included in the final mask if they were significantly active in >90% of all participants. Finally, active voxels were defined as a cluster if they were contiguous and formed a volume of at least 200 μL. Eight cortical regions of interest were identified by using this process (Fig 1 and Table 3).

Anatomic designations were assigned to the regions of interest according to the region-of-interest center in Talairach coordinates. This empirically defined mask was then applied to the results from the individual multiple regression analyses in the current study sample transformed to standard stereotaxic space, by using the fully automated 3dmaskave plug-in in AFNI. This program allows one to compute the average over a region of interest of all voxel values from an input dataset. Average unthresholded *t* values within each region of interest for each person were used as measures of task-related activation intensity in subsequent analyses for hypothesis testing. These 8 a priori regions of interest were used because they represented the most stable activation pattern in response to the task used in this study from a similar yet separate sample of participants.

Data Analyses

Neuropsychological measures were grouped into 1 of 5 cognitive domains: 1) global cognitive functioning, 2) language functions, 3) visual-spatial abilities, 4) memory functions, and 5) attention-executive-psychomotor functions. The following test scores were included in each domain, and raw total scores were used unless otherwise stated: 1) global: MMSE and WASI full-scale IQ; 2) language: WASI Vocabulary subtest and Category Fluency for Animals; 3) visual-spatial: RCF copy and WASI Matrix Reasoning subtest; 4) memory: CVLT-II immediate recall, delayed recall, and recognition discrimination; RCF immediate recall, delayed recall, and recognition discrimination; 5) attention-executive-psychomotor functions: Trail Making A and B time to completion, Controlled Oral Word Association Test, WAIS-III Digit Span subtest, and Grooved Pegboard-Dominant Hand time to completion. Participant raw test scores were converted to z scores by using the study sample mean and SD. Timed test scores were multiplied by −1 so that higher scores indicated better performance. Five
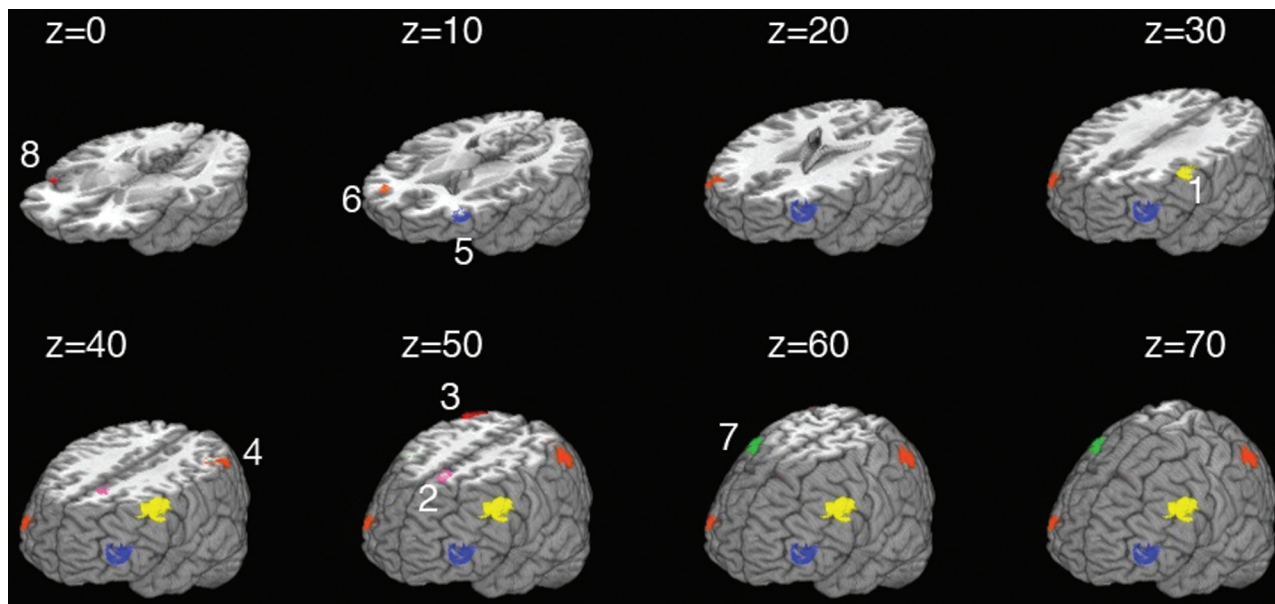
Fig 1. Regions of interest on template anatomy: 1 = left middle frontal gyrus, 2 = left medial frontal/superior frontal gyrus, 3 = right superior parietal lobule, 4 = left inferior parietal lobule, 5 = left middle frontal gyrus, 6 = right superior frontal gyrus, 7 = right middle frontal gyrus, 8 = right inferior frontal gyrus.

Table 3: Comparison of averaged task-related brain activation between adults with MetS and controls in a priori regions of interest (MetS < controls)

Anatomic Region	|X|	Y	Z	Size (mm^3)	P Value
1) Left middle frontal gyrus	33	4	56	2429	.219
2) Left medial frontal/superior frontal gyrus	5	19	44	1651	.261
3) Right superior parietal lobule	37	−63	53	1592	.009[a]
4) Left inferior parietal lobule	49	−52	44	1406	.009[a]
5) Left middle frontal gyrus	44	45	13	1142	.764
6) Right superior frontal gyrus	33	48	15	994	.012[a]
7) Right middle frontal gyrus	32	5	55	676	.104
8) Right inferior frontal gyrus	47	14	3	335	.625

[a] Significant.

composite cognitive domain z scores were calculated for each participant by averaging the z scores of all tests within that domain.

All variable distributions were examined by using the Shapiro-Wilk test of normality recommended for small samples. Demographic and physiologic differences between the metabolic syndrome and control groups were assessed by using nonparametric Mann-Whitney U tests due to the fact that many physiologic variables have naturally skewed distributions. Group differences in functional brain activation within the 8 regions of interest were assessed by using analysis of variance. All statistical analyses were performed by using the Statistical Package for the Social Sciences, Version 16.0 (SPSS, Chicago, Illinois). An α level of .05 was set as the criterion for statistical significance.

Results

Descriptive Statistics

Means and SDs of the demographic and physiologic variables for each group are reported in Table 1. Descriptive statistical analyses revealed an ethnically diverse middle-aged sample, well representative of the population of Texas where the study was conducted based on 2000 census data for the state. Nineteen participants fulfilled criteria for inclusion in the MetS group (48%). The remaining 21 participants (52%) were classified as controls. Sex distributions in the 2 groups were com-

parable ($\chi^2 = 2.63$, $df = 1$, $P = .105$). As expected, the 2 groups exhibited significantly different systolic and diastolic blood pressures, fasting glucose, BMI, triglyceride, and HDL cholesterol values (Table 1). However, there were no significant group differences in age or education (Table 1). There were also no significant differences in global cognitive function, memory, language, visuospatial ability, attention-executive-psychomotor performance, reported depressive symptoms, or 2-back performance between the adults with MetS and controls (Table 2).

Functional Brain Activation and MetS

2-Back-related activation intensities in the left middle frontal gyrus, right superior frontal gyrus, and right middle frontal gyrus were logarithmically transformed before inclusion in the parametric analysis of variance due to a significant skew in the distributions (Shapiro-Wilk > 0.937, $P < .05$). Analysis of variance revealed that MetS was associated with significantly lower task-related activation intensity in the right superior frontal gyrus ($F(1,38) = 6.91$, $P = .012$), right superior parietal lobule ($F(1,38) = 7.65$, $P = .009$), and left inferior parietal lobule ($F(1,38) = 7.56$, $P = .009$) (Table 3 and Fig 2). These relationships remained unchanged even after additional adjustment for any potential effects of antihypertensive medica-
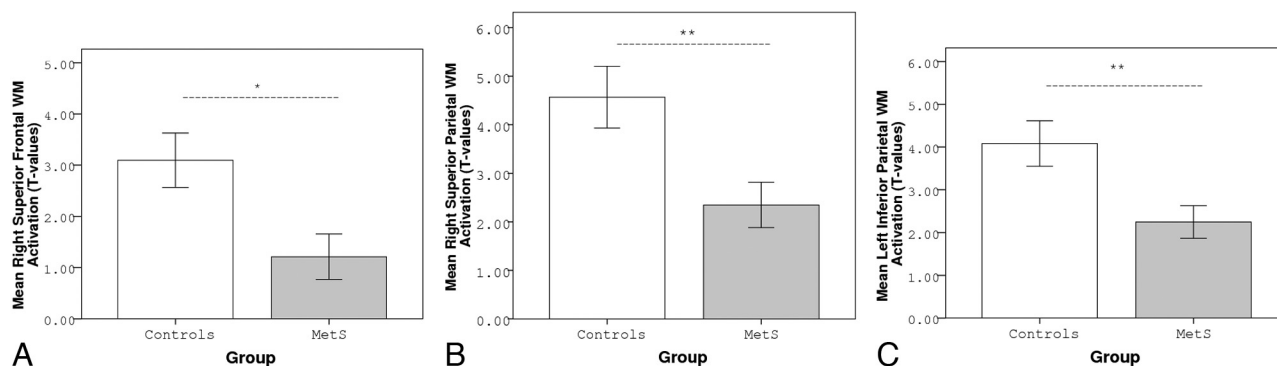
Fig 2. Reduced right superior frontal (*A*), right superior parietal (*B*), and left inferior parietal (*C*) working memory activation in middle-aged adults with MetS compared with age-matched controls. Bars and whiskers represent means and standard errors of the mean. Asterisks indicate significance at *P* < .05; double asterisks indicate significance at *P* < .01.

tion: $F(2,37) = 4.68$, $P = .015$, $F(2,37) = 5.35$, $P = .009$, $F(2,37) = 3.96$, $P = .028$; lipid-lowering medication: $F(2,37) = 3.40$, $P = .044$, $F(2,37) = 3.80$, $P = .032$, $F(2,37) = 4.17$, $P = .023$; or hypoglycemic agents: $F(2,37) = 3.37$, $P = .045$, $F(2,37) = 4.00$, $P = .027$, $F(2,37) = 4.16$ $P = .023$.

Lower functional activation in the right superior parietal and left inferior parietal lobules was significantly related to longer/slower reaction times ($r = -0.35$, $P = .035$ and $r = -0.34$, $P = .037$, respectively). In addition, higher functional activation in the left inferior parietal lobule was significantly related to better task accuracy ($r = 0.36$, $P = .03$). Trends in a similar direction were found between higher functional activation and better task performance in the right superior parietal lobule ($r = 0.30$, $P = .08$) and the right superior frontal gyrus ($r = 0.32$, $P = .05$).

Discussion

The salient finding of the present study is that compared with age- and performance-matched healthy controls, middle-aged individuals with MetS demonstrated significantly lower BOLD response to a working memory task on fMRI. A working memory task was specifically chosen because it engages cognitive processes, such as executive function and attention, known to be especially susceptible to vascular cognitive impairment for which MetS is an important risk factor.[17] We found that diagnosis of MetS was associated with significantly lower task-related BOLD response in the right superior frontal gyrus, right superior parietal lobule, and left inferior parietal lobule despite intact global cognitive performance. One possible interpretation of these early alterations in the cerebrovascular response to cognition in MetS is that they represent early vulnerability of the frontoparietal executive system to metabolic disturbances. The system is involved in regulating attention, switching attentional focus, and task preparation[42] and is known to be affected early in the development of vascular cognitive impairment.[43-45] This interpretation is supported by our present finding that greater task-related BOLD response in these regions was associated with better task performance and faster reaction times. The cross-sectional nature of our study limits our ability to infer future cognitive trajectories from the observed functional activation changes. Longitudinal studies that begin in midlife could help validate the use of BOLD fMRI markers as indicators of long-term cognitive outcomes.

To the best of our knowledge, this is the first study to ex-

amine functional imaging differences during a cognitive challenge in MetS, extending the currently available literature documenting structural changes on neuroimaging[19-21] and cognitive vulnerability in old age.[9-16] A particularly notable aspect of the present study is that MetS-related differences in BOLD response to a demanding cognitive challenge were detected in participants without clinically significant cognitive dysfunction. As evidenced by the widely used exercise stress test, dysfunction in physiologic systems is more likely to manifest when the system is stressed. Early detection of the effects of MetS in middle age by using a cognitive challenge as a stressor has the potential to identify those who may benefit from interventions to halt or delay potentially deleterious effects on the brain. The early cerebrovascular changes we identified highlight the fact that MetS has an impact on cerebral health well before behavioral performance is impaired. These results suggest that developing early interventions for MetS may be important. Diet and exercise have been shown to be effective techniques for attenuating the physiologic disturbances associated with MetS. Our results raise the possibility that early application of risk-factor-reduction strategies may be useful not only for improving physiologic health but also for decreasing the risk of cognitive dysfunction across the lifespan.

fMRI has long been recognized as a promising tool for detecting changes in brain function before individuals meet clinical criteria for cognitive impairment.[46] The participants in our MetS group were at increased risk for coronary heart disease and cerebrovascular disease but did not yet have a diagnosis other than MetS. The fact that we observed lower rather than higher BOLD response in this group is also important to consider. In the past, a higher task-related BOLD response at comparable levels of performance in patients with MS, HIV, and genetic risk for AD relative to healthy controls has been observed and interpreted as compensatory overactivation[25,46,47]; however, the opposite trend (ie, lower task-related activation at similar levels of performance) has been noted in patients at high risk for cardiovascular and cerebrovascular disease.[42,48-50] On the basis these observations, it may be that early in the vascular disease process, subclinical reductions in vascular responsivity and endothelial function result in lower, yet sufficient, amounts of oxygen being delivered to activated neurons, thus producing a lower BOLD response to a cognitive challenge despite intact behavioral performance.[48,49] As vascular problems worsen, further declines in cerebrovascular reactivity and microvascular damage likely lead to vascular

cognitive impairment. Support is provided by a growing body of literature documenting that peripheral cardiovascular dysfunction is related to poor cerebrovascular health and diminished cognitive function in older patients with cardiovascular disease.[43-45,51-55] Due to the multifaceted nature of MetS, further research is necessary to explore the contributions of frank vascular disease to the observed cognitive task—related BOLD response changes in midlife. Further exploration of other potential mechanisms such as alterations in cerebral glucose metabolism and inflammation will also be valuable.

While considering future directions, it is important to discuss the strengths and limitations of the present study. An important strength of the study is the thorough characterization of our sample in terms of cognitive and physiologic functioning. The study used a full cognitive battery as well as measures of metabolic and blood pressure function rather than relying on self-reported medical history. The confirmed cognitive and physiologic health status allows us to interpret the detected functional activation changes with greater confidence, without suspecting confounding effects of under-reported or undiagnosed medical conditions or cognitive disorders. On the other hand, the study was limited to a relatively small sample of self-selected community volunteers. Ideally, the external validity of the results should be tested in larger randomly selected community samples. A larger sample would also allow the exploration of the complex interactions between the various components of metabolic syndrome. In addition, concomitant assessments of white matter integrity may be useful in future studies to further elucidate the relationships detected in this study. While overt signs of microvascular damage in early adulthood are rare, small white matter lesions have been reported in randomly selected individuals in their 40s and 50s.[56] Therefore, assessments of white matter integrity may lend further insights into cerebral metabolic health in middle-aged individuals. Additional measures of BOLD response to noncognitive tasks and hypercapnia, on the other hand, can help determine whether the MetS-related alterations in the cerebrovascular support for cognition reported in this study are specific to brain areas critical for cognitive function and/or related to global changes in cerebral perfusion, cerebrovascular reactivity, or cerebrovascular coupling. Finally, it is important to validate the idea that early alterations in cognitive task-related BOLD response may be indicators of a future cognitive trajectory, which should be assessed in longitudinal studies that begin in midlife and track long-term cognitive outcomes.

Conclusions

In summary, we present the first study to examine fMRI in MetS. Our preliminary results indicate that middle-aged individuals with MetS demonstrate significantly lower BOLD response to a working memory challenge. Thus, fMRI may be a helpful tool to identify early cerebrovascular changes associated with MetS. Future studies including BOLD response to cognitive and noncognitive challenges as well as measures of cerebral perfusion and white matter integrity will be important. These approaches will elucidate the physiologic mechanisms underlying the observed alterations in BOLD response to working memory among middle-aged individuals with MetS. Larger sample sizes will allow examination of the indi-

vidual MetS components as well as the cumulative effect of the constellation of symptoms.

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