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Subclinical vascular disease and cerebral glutamate elevation in metabolic syndrome

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Abstract

Metabolic syndrome (MetS), the co-occurrence of obesity, hypertension, hyperglycemia and dyslipidemia, is an important risk factor for diabetes, cardiovascular disease and end-organ damage in the brain. Our goal was to determine if metabolic syndrome (MetS) differentially affects cerebral metabolism in middle-aged adults with varying degrees of subclinical vascular disease. Sixty-five neurologically healthy adults aged 40 to 60 years (19 with MetS and 46 controls) underwent ultrasound examination of carotid artery intima-media thickness (IMT), a measure of peripheral vascular disease, a full neuropsychological evaluation, and a proton magnetic resonance spectroscopy (^1H MRS) scan of occipitoparietal grey matter. The Johnson- Neyman technique and *pick-a-point* approach were used to test if MetS-related neurochemical changes were moderated by IMT. The MetS and control groups were comparable in age, education, gender distribution, average IMT, and cognitive performance. MetS individuals with low IMT values (1 SD below sample mean) demonstrated comparable neurochemical concentrations to the healthy controls ($t = -0.21$, $p = 0.84$, 95 % CI -0.106 to 0.086), while MetS individuals with high IMT values (1 SD above sample mean) exhibited significantly elevated glutamate concentrations ($t = 2.84$, $p = 0.006$, 95 % CI 0.038 to 0.220). We found that the level of peripheral atherosclerosis moderated the level of elevation of cerebral glutamate concentrations in patients with MetS. These results suggest that peripheral metabolic dysfunction in midlife likely acts in conjunction with subclinical vascular disease to foster pro-neurotoxic conditions in the central nervous system creating early brain vulnerability.

Disclosures

Ms. Gonzales and Mr. Tarumi reports no disclosures.

Keywords

Atherosclerosis; Brain imaging; Carotid ultrasound; MR spectroscopy; Glutamate; Metabolic syndrome

Introduction

Metabolic Syndrome (MetS), the clustering of obesity, hypertension, hyperglycemia, and dyslipidemia in a single individual (Alberti et al. 2009), is being increasingly recognized as detrimental to cognitive function (Akbaraly et al. 2010; Dik et al. 2007; Gatto et al. 2008; Raffaitin et al. 2011; Vanhanen et al. 2006; Yaffe et al. 2009), in addition to its well-established impact on cardiovascular morbidity and mortality (Lau 2009). MetS is now one of an emerging class of neurological disorders related to rapid changes in lifestyle and environment including reduced physical activity, poor nutrition and pollution (Block and Calderon-Garciduenas 2009; Kanoski and Davidson 2011; Sofi et al. 2011). Preliminary studies have linked MetS to silent ischemic brain lesions and early white matter deterioration (Bokura et al. 2008; Park et al. 2008; Segura et al. 2009), diminished functional brain activation (Hoth et al. 2011), and alterations in cerebral neurochemistry (Haley et al. 2010a) similar to those seen in individuals at risk for Alzheimer's disease (Kantarci et al. 2000). However, the neural and cognitive consequences of MetS, and the conditions under which the syndrome creates or fosters early brain vulnerability are not yet fully characterized. The focus of the present study was to determine if MetS differentially affected cerebral metabolism in middle-aged adults with varying degrees of subclinical vascular disease. We chose to test subclinical vascular disease, more specifically, carotid artery intima-media thickness (IMT), as a moderator of MetS-related brain vulnerability due to its recognized role as an independent risk factor for end-organ damage in the brain in asymptomatic patients (Nguyen-Thanh and Benzaquen 2009).

Methods

Participants

Sixty-five community-dwelling adults aged 40–60 years old were studied. The project was advertised in a local newspaper as well as on-line. Participants with hypertension and diabetes were especially solicited to ensure adequate enrollment in the MetS group. Targeted recruitment of minority participants was used to create a sample representative of the demographic characteristics of the state. The study included 42% Caucasian, 45% Hispanic, 10% African-American, and 3 % Other/Did Not Specify individuals.

Exclusion criteria were: 1) neurological disease (i.e., large vessel stroke, seizure disorder, Parkinson's disease, clinically significant traumatic brain injury, multiple sclerosis, or brain infection/meningitis); 2) major psychiatric illness (e.g., schizophrenia, bipolar disorder); 3) substance abuse (diagnosed abuse and/or previous hospitalization for substance abuse); 4) MRI contraindications. To be included in the final analysis, datasets also had to meet MRS data quality standards (Cramer-Rao Lower Bounds for NAA, mI, Cho or Glu <12). Details regarding the demographic and physiological characteristics of the sample can be found in Table 1.

Procedures

The local Institutional Review Board approved all study procedures. Volunteers provided their written informed consent prior to the first study visit. Once enrolled, participants

completed three study visits on separate days: a general health screening and ultrasound imaging, a full neuropsychological evaluation, and brain MRI imaging.

General health assessment and metabolic syndrome classification—Health assessment procedures were conducted as previously described (Haley et al. 2010a). Fasting blood concentrations of glucose, triglyceride, HDL-cholesterol, and LDL-cholesterol were determined using standard enzymatic techniques; arterial blood pressure was measured using a standard oscillometric blood pressure monitor after at least 15 min of rest; and prescription medications were coded as present or absent according to participant self-report. A research assistant later classified medications as antihypertensive, lipid lowering, hypoglycemic, antiplatelet, anti-inflammatory, antidepressant, antihistamine, hormone replacement, or bisphosphonates.

Metabolic syndrome (MetS) was defined as three or more of the following: abdominal obesity {BMI >30, equivalent to waist circumference 94 cm for men and 80 cm for women, (Alberti et al. 2009)}; elevated triglycerides (≥ 150 mg/dL) or treatment for elevated triglycerides; reduced high-density lipoprotein cholesterol (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 mmHg and/or diastolic blood pressure ≥ 85 mmHg) or antihypertensive drug treatment; elevated fasting glucose (≥ 100 mg/dL) or treatment with a hypoglycemic agent.

Ultrasound examination and IMT data processing—Ultrasound images of the carotid artery were obtained using an iE 33 Ultrasound System equipped with a high-resolution linear-array transducer (Philips, Bothell, Washington) as previously described (Tanaka et al. 2002). A longitudinal image (B-mode) of the cephalic portion of the common carotid artery was acquired at 90° to the vessels thus making the near and far wall interfaces clearly perceptible. These ultrasound-derived images were saved in DICOM format. Computerized image-analysis software (Vascular Research Tool Carotid Analyzer, Medical Imaging Applications, Coralville, IA) was used for ultrasound image analysis. Carotid IMT was defined as the distance between the leading edge of the lumen-intima interface and the leading edge of the media-adventitia interface of the far wall. The final IMT value was derived using the average of at least 10 measurements. The same investigator, who was blinded to subject characteristics, performed all image analyses.

Neuropsychological evaluation—Participants completed comprehensive neuropsychological assessment including measures of cognitive and emotional functioning. A detailed description of the cognitive battery and data reduction strategy has been previously published (Haley et al. 2010a). Briefly, to minimize Type I error associated with multiple comparisons, we combined tests assessing similar cognitive functions into five cognitive domains: global, memory, language, visual-spatial, and attention-executive. To achieve that, we converted individual test scores into z-scores using the study's sample mean and standard deviation, multiplied scores of timed tests by -1 to ensure that higher scores always denote better performance, and averaged the z-scores within each domain. A list of test scores included within each domain is available in Table 2.

¹H-magnetic resonance spectroscopy—Brain imaging for each participant was completed on a 3T GE Signa Excite MRI scanner equipped with a standard head coil. Scan session included 3D high-resolution Spoiled Gradient Echo (SPGR) sagittal images of the entire brain (256×256 matrix, FOV=24×24 cm², 1 mm slice thickness, 0 gap) for spectroscopy voxel localization and a PROBE-P ¹H MRS sequence (echo time/ repetition time TE/TR=35/3000 ms, 128 excitations, 5000 Hz spectral width). Data were acquired

from a 6 cm³ volume localized in occipitoparietal grey matter including posterior cingulate gyrus. As in our prior studies (Haley et al. 2010a, b), we focused on occipitoparietal grey matter (Fig. 1) because spectroscopically detectable changes in the neurochemical composition of this region correspond in proportion to severity of cognitive impairment in clinical populations (Kantarci et al. 2000). We used the commercially available software LCModel to identify and quantify metabolite resonances (Provencher 1993). In accordance with standard clinical quantification techniques, the concentrations of neurometabolites are reported as ratios relative to creatine (Cr) (Kantarci et al. 2000). Metabolites of interest included: N-acetyl-aspartate (NAA), a marker of neuronal viability; choline containing compounds (free choline, phosphocholine, and glycerophosphocholine, Cho), markers of membrane breakdown and turn over; myo-inositol (mI), an organic osmolyte and substrate for the synthesis of the secondary messenger, inositol triphosphate; and glutamate (Glu), a marker of excitatory neurotransmission and synaptic integrity (Danielsen and Ross 1999; Ross 1991).

Data analyses

All variable distributions and regression residuals were examined using the Shapiro-Wilk test of normality, recommended for small samples. Demographic and physiologic differences between the MetS and control groups were assessed using non-parametric Kolmogorov-Smirnov tests, which are sensitive to differences in both the location and shape of the empirical distribution functions of two samples. The moderating effect of IMT on the relationship between MetS status and cerebral metabolite concentrations was explored using the Hayes and Matthes's MODPROBE macro for SPSS (Hayes and Matthes 2009). The macro uses two different approaches to assess rigorously the interactions in linear models without unnecessarily dichotomizing a continuous moderator variable. The two approaches are: the Johnson-Neyman (J-N) technique, which identifies the sub-ranges of the moderator variable where the effect of the focal predictor on the outcome is significant versus those where it is not, and the *pick-a-point* approach, which estimates the effect of the focal predictor on the outcome at several representative values of the moderator. Since there are no non-arbitrary guidelines for selecting points within a non-clinical sample of IMT values, we used the macro's default point selection of low (one SD below the sample mean), moderate (the sample mean), and high (one SD above the sample mean) values of the moderator. All statistical analyses were performed using SPSS 19.0 (IBM Corporation, Chicago, IL).

Results

Descriptive statistics

Demographic and physiological variables for each group are reported in Table 1. Descriptive statistical analyses revealed an ethnically diverse, middle-aged sample, representative of the population of the state 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 (29 %). The remaining forty-six participants (71 %) were classified as controls. Gender distributions in the two groups were comparable ($\chi^2=0.12$, $df=1$, $p=0.724$) and there were no significant group differences in age, education or carotid IMT (Table 1). As expected, the two groups exhibited significantly different fasting glucose levels, BMI, triglyceride, and HDL-cholesterol values (Table 1). Three participants in the control group and eight participants in the MetS group were currently being treated with antihypertensive medication; one participant in the control group and three participants in the MetS group were taking lipid-lowering drugs; and four participants in each group were being treated with hypoglycemic agents. Thyroid medication, bisphosphonates, psychoactive medication and vitamins were reported at low frequency (2).

Metabolic syndrome and cognitive function

Raw cognitive test scores and self-reported depressive symptoms are reported in Table 2. To reduce the number of comparisons, we combined multiple measures into five cognitive domain scores (see Method). There were no significant differences in global cognitive function, memory, language, visuo-spatial ability, attention-executive-psychomotor performance or reported depressive symptoms between the adults with MetS and controls (Table 2).

Metabolic syndrome, cerebral metabolism and IMT

Neurometabolite concentrations for the MetS and control groups are presented in Table 1. MetS diagnosis was significantly associated with higher cerebral Glu/Cr ($p=0.034$) as well as higher mI/Cr ($p=0.034$). However, the effect of MetS on Glu/Cr appeared to be moderated by IMT ($F(3,61)=8.28$, $p=0.0001$, MetS $\times$ IMT beta=0.48, $t=2.19$, $p=0.032$, Fig. 2). When the effect of MetS on Glu/Cr was estimated for low IMT values (IMT=0.43 mm), it was found to be non-significant ($t=-0.21$, $p=0.84$, 95 % CI -0.106 to 0.086). A trend towards a significant effect of MetS on Glu/Cr was found at medium IMT values (IMT=0.57 mm, $t=1.74$, $p=0.088$, 95% CI -0.009 to 0.129), and a significant effect of MetS status on Glu/Cr was detected at high IMT values (IMT=0.72 mm, $t=2.84$, $p=0.006$, 95 % CI 0.038 to 0.220). The effect of MetS on mI/Cr followed a similar pattern, though the interaction term in the linear model did not quite reach statistical significance ($F(3,61)=2.33$, $p=0.084$, MetS $\times$ IMT beta=0.28, $t=1.81$, $p=0.075$). The effect of MetS on mI/Cr was non-significant ($t=0.09$, $p=0.928$, 95 % CI -0.066 to 0.072) for low IMT values (IMT=0.43 mm), a trend for medium IMT values (IMT=0.57 mm, $t=1.80$, $p=0.078$, 95 % CI -0.005 to 0.094), and significant at high IMT values (IMT=0.72 mm, $t=2.61$, $p=0.011$, 95 % CI 0.020 to 0.152).

Discussion

In this study, we found that the level of peripheral atherosclerosis moderated elevation of cerebral glutamate concentrations in patients with MetS. While MetS patients with relatively low burden of peripheral atherosclerosis (one SD below the sample mean) had cerebral glutamate concentrations comparable to those of control participants ($p=0.838$, Fig. 2), MetS patients with relatively high burden of vascular disease (one SD above the sample mean) had significantly elevated cerebral glutamate ($p=0.006$, Fig. 2). Our results show that, even at subclinical levels {IMT <0.9 mm (Van Bortel 2005)}, the greater the burden of peripheral vascular disease, the higher the risk of MetS-related neurochemical alterations such as increased glutamate concentrations. Glutamate, though essential for cognitive function (Riedel et al. 2003), is also a well-recognized endogenous neurotoxin (Lipton and Rosenberg 1994). High cerebral glutamate levels promote pathological over-stimulation of glutamate receptors that allow high levels of calcium ions to enter into the cell, initiating structural damage and accelerating cell death (Lipton and Rosenberg 1994). These findings suggest that: 1) brain vulnerability in MetS (Haley et al. 2010a) may be specific to a sub-set of MetS patients with comorbid subclinical atherosclerosis; and 2) peripheral atherosclerosis as measured by carotid IMT appears to be an independent risk factor for potential MetS-related brain damage.

While the concept of IMT as an independent risk factor for end-organ damage in the brain in asymptomatic patients might seem novel, this idea is supported by current research (Nguyen-Thanh and Benzaquen 2009) and reinforced by the recent consensus statement (Stein et al. 2008) that establishes IMT as a sensitive, noninvasive method to quantify subclinical vascular disease independent of traditional risk factors such as those included in the MetS definition (e.g., obesity, hypertension, diabetes, etc.). IMT's particular relevance to brain health is also in line with recent reports relating increases in IMT to cognitive decline

in patients with cardiovascular disease (Haley et al. 2007; Talelli et al. 2004) as well as community dwelling adults (Romero et al. 2009; Sander et al. 2010; Wendell et al. 2009). Furthermore, increased IMT was recently associated with neurochemical alterations in middle-aged individuals (Haley et al. 2010b). Taken together, the current literature is consistent with the notion that IMT could moderate the relationships between MetS and neurochemical markers of brain vulnerability.

In the present study, the modulating effect of MetS on cerebral metabolism with varying degree of IMT was most clearly evident when cerebral glutamate concentrations were examined. Glutamate is a marker of excitatory neurotransmission and synaptic integrity (Danielsen and Ross 1999; Ross 1991) and is involved in the pathogenesis of neurodegenerative disorders and stroke. The mechanisms by which MetS and arterial wall thickening may act synergistically to produce pathological alterations in cerebral glutamate concentrations are unknown. To date, extracellular accumulations of glutamate and lactate have been well documented only in conditions of severe cerebral ischemia (Hossmann 1994). In addition, functional and biochemical studies have shown that long-term exposure to hyperglycemia in animal models of diabetes mellitus are associated with important glutamate receptor abnormalities such as impaired AMPA receptor modulation and reduced NMDA NR2B receptor subunit expression (Chabot et al. 1997; Di Luca et al. 1999). Our results extend the existing literature by providing an indication of cerebral glutamate system dysregulation at earlier stages of hypoperfusion and earlier stages of metabolic disturbance – none of our participants had documented ischemic episodes and only a few had a diagnosis of diabetes. Our findings support recent reports of resting cerebral blood flow reductions in adults with subclinical IMT increases but without identified cerebrovascular disease (Sojkova et al. 2010) as well as evidence of plasma glutamate accumulations in adults with insulin resistance (Tai et al. 2010). In animal models, glutamate induces oxidative stress-related endothelial death (Parfenova et al. 2006). Endothelial function plays an important role in the pathogenesis of MetS and in the initiation of atherosclerosis as measured by IMT (Tai et al. 2010). It is also involved in the regulation of cerebral blood flow. We have recently reported an association between flow-mediated dilation, a peripheral marker of endothelial function, and cerebrovascular response to a cognitive task (Gonzales et al. 2010). Yet, it remains unclear how MetS, IMT, and cerebral glutamate are interrelated in the pathophysiology of cognitive dysfunction. Ideally, future studies would include longitudinal tracking of changes in IMT in relation to both cerebral blood flow and neurochemical alterations in order to determine if the relationship between increased IMT and higher glutamate concentrations observed in this study is mediated by reduced cerebral blood flow and whether they lead to cognitive dysfunction.

The primary limitation of this study is that its conclusions derive from a relatively small sample of community volunteers. A larger sample would enable the exploration of the complex interactions between the various components of MetS, an endeavor beyond the scope of the present project. Furthermore, we need to consider the constraints of our imaging methods. Our volume of interest at the occipitoparietal junction, a standard area used to represent grey matter composition, has the inherent drawback of including white matter because of its relatively large volume. Future studies should include tissue segmentation of the volume of interest as well as additional regions of interest to examine regional and tissue type variations in cerebral metabolite concentrations related to MetS. Additionally, absolute quantification of metabolites in lieu of ratios will facilitate uncovering the significance of the detected changes in metabolite ratios. Finally, our cross-sectional methodology limits our ability to predict future cognitive decline from the detected neurochemical changes. Longitudinal studies that follow participants from mid-life into older age can help validate the use of cerebral metabolite concentrations as predictors of long-term cognitive health.

Summary and conclusions

In summary, we found that the level of peripheral atherosclerosis moderated the level of elevation of cerebral glutamate concentrations in patients with MetS. These results suggest that peripheral metabolic dysfunction in midlife likely acts in conjunction with subclinical vascular disease to foster proneurotoxic conditions in the central nervous system creating early brain vulnerability.

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References

- Akbaraly TN, Kivimaki M, Shipley MJ, Tabak AG, Jokela M, Virtanen M, Marmot MG, Ferrie JE, Singh-Manoux A. Metabolic syndrome over 10 years and cognitive functioning in late midlife: the Whitehall II study. *Diabetes Care*. 2010; 33(1):84–89. [PubMed: 19837794]
- Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JJ, Donato KA, Fruchart J-C, James WPT, Loria CM, Smith SC. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009; 120(16):1640–1645. [PubMed: 19805654]
- Block ML, Calderón-Garcidueñas L. Air pollution: mechanisms of neuroinflammation and CNS disease. *Trends Neurosci*. 2009; 32((9)):506–516. [PubMed: 19716187]
- Bokura H, Yamaguchi S, Iijima K, Nagai A, Oguro H. Meta-bolic syndrome is associated with silent ischemic brain lesions. *Stroke*. 2008; 39(5):1607–1609. [PubMed: 18323475]
- Chabot C, Massicotte G, Milot M, Trudeau F, Gagné J. Impaired modulation of AMPA receptors by calcium-dependent processes in streptozotocin-induced diabetic rats. *Brain Res*. 1997; 768(1–2): 249–256. [PubMed: 9369322]
- Danielsen, ER.; Ross, B. Magnetic resonance spectroscopy diagnosis of neurological diseases. New York: Marcel Dekker, Inc.; 1999.
- Di Luca M, Ruts L, Gardoni F, Cattabeni F, Biessels GJ, Gispen WH. NMDA receptor subunits are modified transcriptionally and post-translationally in the brain of streptozotocin-diabetic rats. *Diabetologia*. 1999; 42(6):693–701. [PubMed: 10382589]
- Dik MG, Jonker C, Comijs HC, Deeg DJH, Kok A, Yaffe K, Penninx BW. Contribution of metabolic syndrome components to cognition in older individuals. *Diabetes Care*. 2007; 30(10):2655–2660. [PubMed: 17563341]
- Gatto NM, Henderson VW, St John JA, McCleary C, Hodis HN, Mack WJ. Metabolic syndrome and cognitive function in healthy middle-aged and older adults without diabetes. *Neuropsychol Dev Cog B Neuropsychol Cog*. 2008; 15(5):627–641.
- Gonzales MM, Tarumi T, Tanaka H, Sugawara J, Swann-Sternberg T, Goudarzi K, Haley AP. Functional imaging of working memory and peripheral endothelial function in middle-aged adults. *Brain Cogn*. 2010; 73(2):146–151. [PubMed: 20493622]
- Haley AP, Forman DE, Poppas A, Hoth KF, Gunstad J, Jefferson AL, Paul RH, Ler AS, Sweet LH, Cohen RA. Carotid artery intima-media thickness and cognition in cardiovascular disease. *Int J Cardiol*. 2007; 121(2):148–154. [PubMed: 17196687]

- Haley AP, Gonzales MM, Tarumi T, Miles SC, Goudarzi K, Tanaka H. Elevated cerebral glutamate and myo-inositol levels in cognitively normal middle-aged adults with metabolic syndrome. *Metab Brain Dis.* 2010a; 25(4):397–405. [PubMed: 21063759]
- Haley AP, Tarumi T, Gonzales MM, Sugawara J, Tanaka H. Subclinical atherosclerosis is related to lower neuronal viability in middle-aged adults: A ^1H MRS study. *Brain Res.* 2010b; 1344:54–61. [PubMed: 20460114]
- Hayes AF, Matthes J. Computational procedures for probing interactions in OLS and logistic regression: SPSS and SAS implementations. *Behav Res Methods.* 2009; 41(3):924–936. [PubMed: 19587209]
- Hossmann KA. Viability thresholds and the penumbra of focal ischemia. *Ann Neurol.* 1994; 36(4):557–565. [PubMed: 7944288]
- Hoth KF, Gonzales MM, Tarumi T, Miles SC, Tanaka H, Haley AP. Functional MR imaging evidence of altered functional activation in metabolic syndrome. *Am J Neuroradiol.* 2011; 32(3):541–547. [PubMed: 21183618]
- Kanoski SE, Davidson TL. Western diet consumption and cognitive impairment: Links to hippocampal dysfunction and obesity. *Physiol Behav.* 2011; 103(1):59–68. [PubMed: 21167850]
- Kantarci K, Jack CR, Xu YC, Campeau NG, O'Brien PC, Smith GE, Ivnik RJ, Boeve BF, Kokmen E, Tangalos EG, et al. Regional metabolic patterns in mild cognitive impairment and Alzheimer's disease: a ^1H MRS study. *Neurology.* 2000; 55(2):210–217. [PubMed: 10908893]
- Lau DCW. Metabolic syndrome: perception or reality? *Curr Atheroscler Rep.* 2009; 11(4):264–271. [PubMed: 19500489]
- Lipton SA, Rosenberg PA. Excitatory amino acids as a final common pathway for neurologic disorders. *N Engl J Med.* 1994; 330(9):613–622. [PubMed: 7905600]
- Nguyen-Thanh HT, Benzaquen BS. Screening for subclinical coronary artery disease measuring carotid intima media thickness. *Am J Cardiol.* 2009; 104(10):1383–1388. [PubMed: 19892054]
- Parfenova H, Basuroy S, Bhattacharya S, Tcheranova D, Qu Y, Regan RF, Leffler CW. Glutamate induces oxidative stress and apoptosis in cerebral vascular endothelial cells: contributions of HO-1 and HO-2 to cytoprotection. *Am J Physiol-Cell Physiol.* 2006; 290(5):C1399–C1410. [PubMed: 16371440]
- Park K, Yasuda N, Toyonaga S, Tsubosaki E, Nakabayashi H, Shimizu K. Significant associations of metabolic syndrome and its components with silent lacunar infarction in middle aged subjects. *J Neurol Neurosurg Psychiatry.* 2008; 79(6):719–721. [PubMed: 18270234]
- Provencher SW. Estimation of metabolite concentrations from localized in vivo proton NMR spectra. *Magn Reson Med.* 1993; 30(6):672–679. [PubMed: 8139448]
- Raffaitin C, Féart C, Le Goff M, Amieva H, Helmer C, Akbaraly TN, Tzourio C, Gin H, Barberger-Gateau P. Metabolic syndrome and cognitive decline in French elders: the Three-City Study. *Neurology.* 2011; 76(6):518–525. [PubMed: 21288982]
- Riedel G, Platt B, Micheau J. Glutamate receptor function in learning and memory. *Behav Brain Res.* 2003; 140(1–2):1–47. [PubMed: 12644276]
- Romero JR, Beiser A, Seshadri S, Benjamin EJ, Polak JF, Vasan RS, Au R, DeCarli C, Wolf PA. Carotid artery atherosclerosis, MRI indices of brain ischemia, aging, and cognitive impairment: the Framingham study. *Stroke.* 2009; 40(5):1590–1596. [PubMed: 19265054]
- Ross BD. Biochemical considerations in ^1H spectroscopy. Glutamate and glutamine; myo-inositol and related metabolites. *NMR Biomed.* 1991; 4(2):59–63. [PubMed: 1677586]
- Sander K, Bickel H, Förstl H, Etgen T, Briesenick C, Poppert H, Sander D. Carotid-intima media thickness is independently associated with cognitive decline. The INVADE study. *Int J Geriatr Psychiatry.* 2010; 25(4):389–394. [PubMed: 19750556]
- Segura B, Jurado MA, Freixenet N, Falcón C, Junqué C, Arboix A. Microstructural white matter changes in metabolic syndrome: a diffusion tensor imaging study. *Neurology.* 2009; 73(6):438–444. [PubMed: 19667318]
- Sofi F, Valecchi D, Bacci D, Abbate R, Gensini GF, Casini A, Macchi C. Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. *J Int Med.* 2011; 269(1):107–117.

- Sojkova J, Najjar SS, Beason-Held LL, Metter EJ, Davatzikos C, Kraut MA, Zonderman AB, Resnick SM. Intima-media thickness and regional cerebral blood flow in older adults. *Stroke*. 2010; 41(2): 273–279. [PubMed: 20044526]
- Stein JH, Korcarz CE, Hurst RT. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American society of Echocardiography carotid intima-media thickness task force. *J Am Soc Echocardiogr*. 2008; 21(4): 93–111. [PubMed: 18261694]
- Tai ES, Tan MLS, Stevens RD, Low YL, Muehlbauer MJ, Goh DLM, Ilkayeva OR, Wenner BR, Bain JR, Lee JJM, et al. Insulin resistance is associated with a metabolic profile of altered protein metabolism in Chinese and Asian-Indian men. *Diabetologia*. 2010; 53(4):757–767. [PubMed: 20076942]
- Talelli P, Ellul J, Terzis G, Lekka NP, Gioldasis G, Chrysanthopoulou A, Papapetropoulos T. Common carotid artery intima media thickness and post-stroke cognitive impairment. *J Neurol Sci*. 2004; 223(2):129–134. [PubMed: 15337613]
- Tanaka H, Seals DR, Monahan KD, Clevenger CM, DeSouza CA, Dinunno FA. Regular aerobic exercise and the age-related increase in carotid artery intima-media thickness in healthy men. *J Appl Physiol*. 2002; 92(4):1458–1464. [PubMed: 11896010]
- Van Bortel LM. What does intima-media thickness tell us? *J Hypertens*. 2005; 23(1):37–39. [PubMed: 15643121]
- Vanhanen M, Koivisto K, Moilanen L, Helkala EL, Hänninen T, Soininen H, Kervinen K, Kesäniemi YA, Laakso M, Kuusisto J. Association of metabolic syndrome with Alzheimer disease: a population-based study. *Neurology*. 2006; 67(5):843–847. [PubMed: 16966548]
- Wendell CR, Zonderman AB, Metter EJ, Najjar SS, Waldstein SR. Carotid intimal medial thickness predicts cognitive decline among adults without clinical vascular disease. *Stroke*. 2009; 40(10): 3180–3185. [PubMed: 19644063]
- Yaffe K, Weston AL, Blackwell T, Krueger KA. The metabolic syndrome and development of cognitive impairment among older women. *Arch Neurol*. 2009; 66(3):324–328. [PubMed: 19273750]

Fig. 1. Volume of interest superimposed on high-resolution anatomy and representative spectrum. NAA=N-acetyl aspartate, Glu=glutamate, Cr=creatine +phosphocreatine, Cho=choline containing compounds, ml=myo-inositol

Fig. 2. Interaction plot indicating glutamate elevation in MetS adults with high levels of subclinical atherosclerosis. (Low IMT=0.43 mm; High IMT=0.72 mm)

Table 1

Participants' demographic and physiological characteristics

	Controls (n=46) Mean $\pm$ SD	MetS (n=19) Mean $\pm$ SD	p-value
Male/Female	22/24	10/9	0.724
Age (year)	50.0 $\pm$ 6.5	51.9 $\pm$ 7.0	0.413
Education Level (year)	15.1 $\pm$ 2.5	15.3 $\pm$ 3.1	0.992
Systolic Blood Pressure (mmHg)	122 $\pm$ 14	134 $\pm$ 20	0.090
Diastolic Blood Pressure (mmHg)	74 $\pm$ 8	81 $\pm$ 12	0.101
Body Mass Index (kg/m ²)	26.6 $\pm$ 4.2	34.1 $\pm$ 4.5	0.000
HDL-Cholesterol (mg/dL)	50.4 $\pm$ 14.7	39.4 $\pm$ 12.2	0.021
Triglyceride (mg/dL)	126.7 $\pm$ 64.1	249.5 $\pm$ 98.0	0.000
LDL-Cholesterol (mg/dL)	125.6 $\pm$ 33.4	116.2 $\pm$ 34.6	0.792
Fasting Glucose (mg/dL)	104.1 $\pm$ 44.5	116.7 $\pm$ 40.7	0.004
Number of Risk Factors	1 $\pm$ 0.82	3.5 $\pm$ 0.61	0.000
IMT (mm)	0.56 $\pm$ 0.11	0.61 $\pm$ 0.20	0.413
NAA/Cr	1.40 $\pm$ 0.10	1.43 $\pm$ 0.11	0.369
Cho/Cr	0.18 $\pm$ 0.03	0.19 $\pm$ 0.05	0.538
mI/Cr	0.71 $\pm$ 0.09	0.76 $\pm$ 0.08	0.034
Glu/Cr	1.42 $\pm$ 0.11	1.50 $\pm$ 0.19	0.034

HDL=high-density lipoprotein; LDL=low-density lipoprotein; IMT=carotid artery intima-media thickness; NAA=N-acetyl- aspartate; Cr=creatine +phosphocreatine; Cho=choline +phosphocholine; mI= *myo*-inositol; Glu=glutamate

Table 2**Cognitive and Emotional Functioning**

Test Measures by Domain	Controls (n=46) Mean ± SD	MetS (n=19) Mean ± SD	Total Possible Score	p-value
Global Cognitive Functioning				0.090
Mini Mental Status Exam	28.5±1.4	28.3±1.5	30	
Wechsler Abbreviated Scale of Intelligence	114.2±12.7	106.4±12.9	95 % is 149–160	
Language				.0833
WASI Vocabulary Subtest	65.3±8.8	60.7±10.3	80	
Category Fluency for Animals	23.4±5.5	23.8±6.7	1 min limit	
Visual-Spatial				0.980
Rey Complex Figure Test, Copy	29.9±4.2	31.6±3.4	36	
WASI Matrix Reasoning Subtest	26.2±4.1	24.1±4.8	35 (12–44 years) 32 (45–79 years)	
Memory				0.516
California Verbal Learning Test II				
Immediate Recall	10.4±3.5	10.6±2.7	16	
Delayed Recall	10.8±3.6	11.7±2.4	16	
Recognition (Yes/No)	3.2±2.0	3.9±3.0	–4 to 4	
Rey Complex Figure Test				
Immediate Recall	15.4±5.0	17.6±6.1	36	
Delayed Recall	15.2±5.2	16.6±5.6	36	
Recognition Discrimination	18.8±4.0	20.4±1.5	24	
Attention-Executive-Psychomotor				0.539
Trail Making Test A, Time in seconds	31.8±10.4	32.1±8.7	5 min limit	
Trail Making Test B, Time in seconds	75.0±29.2	77.6±30.0	5 min limit	
Controlled Oral Word Association Test	39.3±10.6	37.0±9.8	3 min limit	
Grooved Pegboard Dominant Hand, Time in seconds	78.1±14.8	73.1±9.2	No limit	
WAIS-III Digit Span Subtest	16.7±4.2	16.5±4.3	30	
Beck Depression Inventory II	5.6±5.8	6.6±6.1	63	