

Cognitive decline in metabolic syndrome is linked to microstructural white matter abnormalities

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Abstract Subjects with metabolic syndrome (MetS) often show worse cognitive performance compared with the healthy population. We investigated whether microstructural white matter abnormalities are associated with cognitive performance in adults with MetS using diffusion tensor MR imaging. A total of 32 subjects with MetS (age 64.8 ± 7.8 , 56.25 % female) and 23 age-, gender-, and education-matched healthy controls completed a battery of neuropsychological tests and diffusion tensor imaging (DTI) at 3-T MRI. Brain global and regional volumes, white matter fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (LD) were calculated. The least-square models adjusted for age, sex, HbA1c, hypertension, body mass index, hyperlipidemia, and white matter hyperintensities were used to evaluate the relationship between cognitive function and DTI. The MetS group had worse performance in verbal fluency (VF) and learning and memory function (total VF: T score ($p = 0.01$), VF: animals T score ($p = 0.0001$), Hopkins Verbal Learning Test (HVL): Total recall

T score ($p = 0.0001$), and HVL: delayed recall T score ($p = 0.002$), as compared with controls. In the MetS group, abnormalities in diffusivity measures were associated with worse cognitive performance [VF: animals T score and left post-central gyrus-LD ($p = 0.0007$, r_{adj} 0.4), R angular gyrus-RD ($p = 0.0008$, r_{adj} 0.3), L supra-marginal gyrus-RD ($p = 0.009$, r_{adj} 0.2) after adjusting for age, sex, HbA1c, 24 h mean BP, presence of hyperlipidemia, and global white matter hyperintensities]. Microstructural white matter abnormalities in the MetS group might be the underlying mechanisms of worse verbal learning and memory performance.

Keywords Metabolic syndrome · Cognitive decline · Diffusion tensor imaging · Microstructural white matter

Introduction

Metabolic syndrome (MetS) is a complex disorder that includes abdominal obesity, glucose intolerance and/or insulin resistance, high blood pressure, and dyslipidemia [1]. MetS as well as its individual components have been identified as important modifiable risk factors for cognitive decline and are associated with cognitive underperformance, mild cognitive impairment, and dementia [2–4]. T2DM, an important cardiovascular risk factor, is linked with cognitive decline, abnormal brain metabolism, and atrophy [5–8]. Diffusion Tensor Imaging (DTI) has been used to quantify microstructural alterations in white matter that may impact cognitive performance [9–11]. DTI-derived metrics of white matter integrity are considered a more sensitive tool compared with structural MRI and might reveal subtle changes before those are detectable by the conventional structural MRI metrics [12].

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The association among individual cardiovascular risk factors and cognitive function has widely been studied [9], but the effect of MetS as a whole on brain structure and cognitive performance has not been well studied [13]. Prior studies that evaluated the impact of MetS on white matter (WM) microstructure have focused on the analyses of the main WM tracts [13, 14] and did not analyze specific brain regions. In addition, a limited number of studies attempting to link the impact of MetS on regional white matter microstructure to worse cognitive performance [15] reported that a fractional anisotropy (FA) decrease is associated to worse processing speed function. In this study, we aimed to determine the impact of MetS on white matter microstructure and cognitive performance in older adults, and a population group consistently linked to the presence of cognitive decline secondary to a higher presence of risk factors (T2DM, hypertension, obesity, and dyslipidemia) [16–19]. We hypothesized that (1) MetS is associated with microstructural white matter abnormalities in the brain, and (2) these abnormalities would be associated with worse cognitive performance in subjects with MetS compared with controls.

Methods

Subjects

This study was a case–control study of cognitive performance coupled with neuroimaging in T2DM vs non-diabetic controls conducted at the Syncope and Falls in the Elderly Laboratory, General Clinical Research Center and at the Center for Advanced Magnetic Resonance Imaging, at the Beth Israel Deaconess Medical Center (BIDMC), between August 2009 and July 2013. Patients underwent an initial visit, followed by a 2-year follow-up visit. The current report is a cross-sectional post hoc analysis of data collected in the baseline visit. Inclusion criteria for the original study were: age 50–85, diagnosis of T2DM and treated for more than 5 years, non-diabetic controls, hypertensive (BP > 140/90 mmHg and/or treated for hypertension), and normotensive (BP < 140/90 mmHg and no medical history of hypertension).

Subjects were originally recruited via local advertisement, and screened by medical history. Subjects that met inclusion/exclusion criteria signed an informed consent form (ICF) as approved by the Institutional Review Board (IRB) at BIDMC.

Exclusion criteria were: type 1 diabetes, acute medical conditions, myocardial infarction or major surgeries in last 6 months, history of stroke, dementia or Mini-Mental State Examination (MMSE) less than 24, carotid stenosis, heart or valvular disease, liver or renal failure or transplant,

severe hypertension (systolic BP > 200 mmHg and/or diastolic BP > 110 mmHg, or treated with three or more antihypertensive medications), seizures, malignant tumors, alcohol abuse, recreational drug use, and morbid obesity (body mass index (BMI) > 40). Magnetic resonance imaging (MRI) exclusion criteria were: metallic bioimplants (e.g., pacemakers and valve replacements not compatible with 3-T MRI guidelines), claustrophobia, or inability to cooperate.

A total of 131 subjects were enrolled, and 75 subjects completed the study. Subjects were excluded for the following reasons: 29 were ineligible after signing ICF for violation of one or more inclusion/exclusion criteria, 10 withdrew consent, 12 were terminated (cancer, inappropriate conduct, hyperglycemia, stroke, arrhythmia, etc.), and 5 were lost to follow-up. Of the 75 patients completing the study, another 20 patients were excluded from the present analysis due to incomplete MRI data sets. We divided the remaining 55 patients of our cohort into two groups, those meeting criteria for MetS and those who were MetS-free (controls). MetS was defined according to the Consensus statement from the International Diabetes Federation [20], which includes the following criteria: increased triglycerides (≥ 150 mg/dl or in treatment), reduced HDL cholesterol (<40 mg/dl in men, <50 mg/dl in women, or in treatment), increased BP (SBP ≥ 130 and/or DBP ≥ 85 mmHg, or in treatment), increased fasting glucose (>100 mg/dl or in treatment), and increased waist circumference (≥ 102 cm in men, ≥ 88 cm in women).

The MetS group included a total of 32 subjects [age 64.8 ± 7.8 , 56.25 % female, 28 T2DM (duration 14.6 ± 8.5 years)] and 23 age-, gender-, and education-matched non-diabetic normotensive controls. Subjects with T2DM were treated for more than 5 years and were either normotensive (blood pressure (BP) <140/90 mmHg and no medical history of hypertension), or hypertensive (BP >140/90 mmHg and/or treated for hypertension). The control group had normal fasting glucose and glycated hemoglobin (HbA1c).

Protocol

All subjects completed a medical history questionnaire, physical, and neurological examinations. Fasting laboratory chemistries were obtained to measure blood glucose, HbA1c, and lipid profile. Twenty-four-hour BP was obtained every 20 min using a wearable 24-h home monitoring device (Dynapulse, Inc. Vista, CA, USA).

Neuropsychological measures

The neuropsychological assessment included executive function [Trial Making Test (TMT); Verbal fluency (VF),

including phonemic and semantic fluency tasks], verbal learning and memory function (Hopkins Verbal Learning Test-Revised (HVLТ), including a Total Recall, Delayed, Retention, and Recognition Discrimination index), a measure of visual-spatial ability and visual memory function (Rey–Osterreith Complex Figure Test (ROCF), including Immediate Recall (I.R.) and Delayed Recall (D.R.) tests), a measure of attention [Digit Span (DS)], and MMSE. The test results were analyzed using age-, gender-, race- and education-adjusted standardized *T* scores.

Magnetic resonance imaging

Magnetic resonance imaging data were acquired using a 3-T, GE GHX MRI scanner with a quadrature and eight channel phase array head coils (GE Medical Systems, Milwaukee, WI, USA). Studies used a 3-D magnetization prepared rapid acquisition with gradient echo (MP-RAGE) and fluid attenuated inversion recovery (FLAIR) sequences to obtain anatomical images. The image analysis was developed using interactive data language (IDL, Research Systems, Boulder, CO, USA) and MATLAB (MathWorks, Natick, MA, USA). T1- and T2-weighted anatomical images (MP-RAGE and FLAIR) were co-registered non-linearly to the MNI152 standard template and segmented to calculate regional gray matter (GM) and white matter (WM) in main anatomical lobes and their subregions (SPM, University College London, UK). MP-RAGE and FLAIR images were co-registered to a standard template and segmented to calculate regional GM, WM, and white matter hyperintensities (WMHs) volume in the frontal, temporal, parietal, and occipital regions using statistical parametric mapping software package (SPM, University College London, UK). WMHs were identified by thresholding of hyperintense pixels on FLAIR images with >30 % increase in signal intensity compared with the global WM average for each patient, and normalized for total brain volume [21].

Diffusion tensor imaging

Diffusion tensor imaging was acquired using a diffusion-weighted (DW)-EPI sequence (TR = 10,000 ms; TE = 80 ms; slice thickness = 5 mm; no gap; in-plane resolution = 1 mm, independent diffusion gradient directions using $b = s/\text{mm}^2$, and one with $b = 0 s/\text{mm}^2$).

Data were preprocessed for head motion, and distortions due to eddy currents. Non-brain tissue was removed using the brain extraction tool (BET) implemented in the FSL package. DTI data were calculated for each voxel after fitting the diffusion tensor model to each voxel using FMRIB's Diffusion Toolbox (FDT) from the FSL package. We used LONI probabilistic brain atlas, which has been

thresholded 50 % of their probability leading to shrinkage of the included ROI and restricted it to white matter boundary. Those ROIs are binarized and transformed to subject's native space using inverse transformation matrix. In each ROI, we extracted fraction anisotropy (FA), mean diffusivity (MD), axial diffusivity (LD), and radial diffusivity (RD).

These diffusion parameters were used as a measure to quantify the integrity of the microstructural WM, since it has been proven that changes in the water diffusion within the tissues are highly predictive of alterations in its microstructural integrity [22].

Statistical analysis

JMP Pro 10.0.0 (SAS Institute, Cary, NC, USA) was used to perform all the statistical analyses. Descriptive analyses were used for demographic characteristics. Demographic data, cognitive function, brain volumes, and DTI metrics were compared between the groups using one-way ANOVA and non-parametric tests. Least-square (LS) models were used to assess the association between DTI metrics, brain volumes, and changes in cognitive function. The models were adjusted for age, sex, HbA1c, 24-h mean BP, BMI, fasting glucose, and the presence of hyperlipidemia and WMHs. Age was included in all the analyses as a covariate to account for differences in WM volume due to age-related decline [23]. Global and regional DTI metrics were used as independent variables. The dependent variables were the cognitive results. We present r^2 adjusted for model covariates and selected r^2 adjusted >0.1, and $p < 0.05$ for a more conservative approach. To minimize repeated-measures effect, each brain region was modeled separately.

Results

Demographic and clinical results

Demographic and clinical characteristics were compared between group using one-way ANOVA and non-parametric tests and are shown in Table 1. The MetS group and the controls did not differ in age, sex, or education years. As expected, subjects with MetS had a significantly greater BMI, 24-h systolic and mean BP, HbA1c, triglycerides, and the presence of hyperlipidemia by medical history, as compared with controls. Subjects with MetS had worse performance on the verbal fluency, learning, and delayed recall tasks [VF: *T* score ($p = 0.01$), VF: animals *T* score ($p \leq 0.0001$), HVLТ: Total Recall *T* score ($p \leq 0.0001$), and HVLТ: Delayed Recall *T* score ($p = 0.003$)], as compared with the controls.

Table 1 Characteristics of the study group

	MetS group (<i>n</i> = 32)	Control group (<i>n</i> = 23)	<i>p</i> value
Demographics			
Age	64.8 ± 7.8	66.9 ± 10.9	NS
Gender (% female)	56.25 %	52.17 %	NS
Body mass index (kg/m ²)	29.8 ± 5.8	25 ± 3.1	0.0003
Education (years)	15 ± 3.1	16 ± 3	NS
Cardiovascular and metabolic outcomes			
Hemoglobin A1c (%)	7.1 ± 1.3	5.7 ± 0.3	<0.0001
Diabetes mellitus type 2 (%)	87.5 %	0 %	
Hypertension (%)	100 %	0 %	
Hyperlipidemia medical history (years)	21 ± 65.63 %	7 ± 30.43 %	0.01
Triglycerides (mg/dL)	142.8 ± 95.6	94.5 ± 42	0.01
HDL (mg/dL)	48.7 ± 16.2	55.1 ± 16.9	NS
24 h systolic blood pressure (mmHg)	133.2 ± 7.3	126.7 ± 8.1	0.008
24 h diastolic blood pressure (mmHg)	71.1 ± 7.1	67.7 ± 8.4	NS
24 h mean blood pressure (mmHg)	91.7 ± 6.5	86.7 ± 7.7	0.01
Imaging characteristics			
Whole brain FA	0.3 ± 0.01	0.3 ± 0.01	NS
Whole brain MD	0.9 ± 0.06	0.9 ± 0.06	NS
Whole brain RD	1.2 ± 0.07	1.1 ± 0.06	NS
Whole brain LD	0.7 ± 0.06	0.7 ± 0.06	NS
Global GM/ICV	0.37 ± 0.05	0.39 ± 0.04	NS
Global WM/ICV	0.25 ± 0.03	0.27 ± 0.02	NS
Global CSF/ICV	0.36 ± 0.07	0.32 ± 0.06	NS
Hippocampus	0.007 ± 0.0009	0.07 ± 0.0009	NS
WMHs	15.6 ± 6.4	12.6 ± 3.9	0.03
L angular gyrus-FA	0.2 ± 0.02	0.3 ± 0.03	0.02
R angular gyrus-FA	0.2 ± 0.03	0.3 ± 0.02	0.03
L post-central gyrus-LD	1.15 ± 0.06	1.11 ± 0.06	0.05
R angular gyrus-RD	0.76 ± 0.08	0.71 ± 0.07	0.04
Cognitive outcomes			
Hopkins Verbal Learning T Score			
Total recall	45.8 ± 12.7	59 ± 8.3	<0.0001
Delayed recall	44.1 ± 12.9	54 ± 10.1	0.002
Retention %	81.5 ± 18.6	89.4 ± 15.2	NS
Recognition discrimination index	47.1 ± 11	52.1 ± 7.3	0.05
Rey–Osterrieth Complex Figure Test T Score			
Immediate recall	42.2 ± 17.2	51.5 ± 16.6	0.05
Delayed recall	43.3 ± 17.1	49.5 ± 16.4	0.1
Verbal Fluency T Score	46.3 ± 10.4	52.3 ± 7.9	0.01
Verbal Fluency: animals T Score	31.6 ± 12.3	48.3 ± 11.3	<0.0001
Trail Making T Score	48.7 ± 12.4	51.3 ± 9.8	NS
Mini-Mental State Examination	28.8 ± 1.3	28.8 ± 1.6	NS

Groups did not differ in normalized global GM, WM volumes, and whole brain DTI metrics. MetS group had greater global WMHs volume ($p = 0.03$). We observed differences in regional DTI metrics in FA, MD, LD, and RD values. The MetS group showed several abnormalities in the angular gyrus in both hemispheres, e.g., lower FA

values in L angular gyrus (0.02) and R angular gyrus (0.03), and higher RD values in R angular gyrus (0.02) and higher LD values in the L post-central gyrus (0.05) (Table 1). No differences between regional GM and WM volumes were observed between the groups.

Associations between microstructural measures and cognition

The relationship between global and regional DTI metrics and cognitive performance was examined using the LS models adjusting for age, mean systolic BP, HbA1c, BMI, presence of hyperlipidemia, and global WMHs volume.

Global DTI metrics and cognitive performance

In the entire cohort, a better performance on the semantic category of the verbal fluency task was positively associated with the whole brain FA, a measure of infrastructural integrity ($r^2_{\text{adj}} = 0.1, p = 0.007$), and negatively with the whole brain MD, an inverse measure of membrane and cellular density [24] ($r^2_{\text{adj}} = 0.1, p = 0.01$), LD ($r^2_{\text{adj}} = 0.09, p = 0.02$), and negatively with RD, a measure of WM de- or dysmyelination ($r^2_{\text{adj}} = 0.1, p = 0.006$). Subjects with MetS had a positive association between the verbal fluency task and whole brain FA ($r^2_{\text{adj}} = 0.2, p = 0.005$), and a negative correlation with MD ($r^2_{\text{adj}} = 0.3, p = 0.001$), LD ($r^2_{\text{adj}} = 0.2, p = 0.004$), and RD ($r^2_{\text{adj}} = 0.3, p = 0.0007$). No similar association was seen in the control group, which might indicate that the deleterious effect of MetS on cognitive performance is mediated through WM microstructure alterations.

Regional DTI metrics and cognitive performance

Table 2 shows the relationships between regional DTI metrics and cognitive performance in the MetS group using four LS models (1–4) adjusting for age, sex, HbA1c, 24-h mean BP, BMI, presence of hyperlipidemia, and global WMHs volume. Significant negative associations were found between the semantic fluency task and WM diffusivity measures, in contrast to the control group in which no significant associations were observed. The strongest associations were found with the WM microstructure of the post-central, supra-marginal, angular and parahippocampal gyri, and the hippocampal region. In model 2, adjusted for age, HbA1c, 24-h mean BP, and global WMHs volume, a lower score in cognitive performance was correlated with higher diffusivity metrics in the L post-central gyrus [LD ($r^2_{\text{adj}} = 0.3, p = 0.006$)], L angular gyrus [RD ($r^2_{\text{adj}} = 0.2, p = 0.03$)], R hippocampus [RD ($r^2_{\text{adj}} = 0.3, p = 0.007$)], R post-central [RD ($r^2_{\text{adj}} = 0.3, p = 0.01$)], R supra-marginal gyrus [RD ($r^2_{\text{adj}} = 0.3, p = 0.007$)], R angular gyrus [RD ($r^2_{\text{adj}} = 0.4, p = 0.0006$)], and L hippocampus [RD ($r^2_{\text{adj}} = 0.2, p = 0.03$)] (Fig. 1). We also found similarly significant associations in models 1, 3, and 4. A negative

HbA1c effect was observed on the VF: animals *T* score and a less intense association between HbA1c and DTI parameters was seen. Similar interaction was observed between a lower HVL: Total Recall *T* score and a higher diffusivity metric in the R angular gyrus [RD ($r^2_{\text{adj}} = 0.2, p = 0.01$)] in the MetS group. In controls, no significant associations between microstructural WM abnormalities and cognitive performance were observed. We also investigated whether there was an association between normalized regional GM in the aforementioned areas and the VF: animals *T* score, using it as a predictive variable in the same 4 models. In models 1, 3, 4, and for most regions in model 2, there was no association between regional GM and cognitive performance. Only for R angular gyrus-RD and L supra-marginal gyrus-RD in model 2, the association was statistically significant.

The critical role of hyperglycemia

In our study, poor glycemic control (HbA1c) was the only metabolic component associated with worse cognitive performance in the univariate analyses (Fig. 2). This suggests that chronic hyperglycemia may be one of the main pathophysiologic mechanisms underlying cognitive decline associated with MetS and is further highlighted in the multiple regression models of Table 2: HbA1c was the only variable that retained a robust independent negative association with cognitive performance, whereas the rest of MetS components (hyperlipidemia, obesity, and hypertension) was not independently associated with either cognitive performance or DTI metrics. The duration of T2DM did not have an impact on our findings, either in univariate or multivariate regression analyses (results not shown). No relation between WMHs and cognition or DTI metrics was observed in our analysis.

We also examined possible associations between global vasoreactivity and gray and white matter volume, as well as global DTI metrics, and did not find one. In addition, we explored the relationship between a panel of inflammatory and other serum biomarkers and cognitive outcomes and imaging metrics and found no significant associations in either group. The panel included C-reactive protein, leptin, insulin-like growth factor-1, interleukin-6, tumor necrosis factor- α , intercellular adhesion molecule-1, and vascular cell adhesion molecule-1.

Discussion

This study evaluated the impact of MetS on brain structure and cognitive performance in older adults and the main findings are: (1) MetS is associated with impaired WM

Table 2 Relationship between cognitive performance and DTI metrics (MetS group)

VF: animals (<i>T</i> score)	L post-central gyrus—LD	L post-central gyrus—RD	R post-central gyrus—RD	L supra- marginal gyrus—LD	L supra- marginal gyrus—RD	L angular gyrus—RD	R angular gyrus—MD	R angular gyrus—RD
LS Model-1								
r^2_{adj}	0.2	0.3	0.1	0.2	0.2	0.1	0.1	0.3
p	0.003	0.001	0.01	0.005	0.009	0.04	0.02	0.0008
HbA1c	0.04	0.01	0.03	0.05	0.02	NS	NS	NS
LS Model-2								
r^2_{adj}	0.3	0.4	0.3	0.3	0.3	0.2	0.3	0.4
p	0.006	0.001	0.01	0.004	0.01	0.03	0.02	0.0006
HbA1c	NS	NS	NS	NS	NS	NS	NS	NS
LS Model-3								
r^2_{adj}	0.2	0.3	0.2	0.2	0.2	NS	0.1	0.3
p	0.003	0.001	0.01	0.007	0.009	NS	0.02	0.001
HbA1c	0.04	0.01	0.03	0.03	0.01	0.05	NS	0.03
LS Model-4								
r^2_{adj}	0.2	0.3	0.1	0.2	0.2	0.1	0.1	0.3
p	0.003	0.001	0.01	0.007	0.009	0.04	0.02	0.001
HbA1c	NS	0.02	0.04	0.03	0.02	NS	NS	0.04

Model 1 adjusted for age, sex, HbA1c, and mean BP, *Model 2* adjusted for age, HbA1c, mean BP and the global WMHs volume, *Model 3* adjusted for age, HbA1c, mean BP, and the presence of hyperlipidemia, *Model 4* adjusted for age, HbA1c, mean BP and BMI, *R* right, *L* left, *VF* verbal fluency, *FA* fractional anisotropy, *MD* mean diffusivity, *LD* axial diffusivity, *RD* radial diffusivity, *LS* least squares

microstructural integrity in the angular, post-central, supra-marginal, parahippocampal gyri, and the hippocampus all of which are key areas of neural networks implicated in verbal learning and memory processing [25–27]. (2) Subjects in the MetS group performed worse in the cognitive domains of verbal fluency and verbal recall compared with controls. (3) This cognitive underperformance was mediated by the microstructural WM abnormalities in specific brain regions. (4) Hyperglycemia was the only MetS component that was associated with abnormal cerebral microstructure integrity as well as worse cognitive performance.

MetS subjects performed markedly worse in specific cognitive domains of verbal fluency and visuospatial memory, as compared with healthy controls. However, their overall results on MMSE (mean 28.8) were similar to controls which would label them as “cognitively intact” [28]. Therefore, it is plausible that older people with MetS may underperform semantic VF and verbal recall, both of which that are considered surrogate markers of executive function and learning and memory [29] and this dysfunction might not be detected using routine clinical bedside testing. Cognitive testing was adjusted for age and education level, thus minimizing the effects of these variables, but the association could be even stronger in the elderly or people with poor control of MetS components (e.g., HbA1c, blood pressure, or morbid obesity).

T2DM, HTN, and other cardiovascular risk factors that are components of MetS have been individually associated with worse cognitive performance [30, 31] and subsequent cognitive decline [32, 33] in prior studies. In our cohort, chronic hyperglycemia (HbA1c), among all MetS components, was the only one that was robustly associated with worse score in the VF test both in univariate and multivariate analyses in our sample. Our MetS group had well-controlled blood pressure (average SBP of 133 mmHg) and relatively good glycemic control (average HbA1c 7.1). Our models were adjusted for the effects of blood pressure, BMI, and hyperlipidemia, but their effects were not significant. It is possible that the impact of hyperglycemia or HTN could be even stronger in a general population sample with less well-controlled vascular risk factors.

Besides cognitive performance, hyperglycemia was also associated with microstructural changes in WM affecting specific brain regions rather than with a global load of WMHs (Table 2). DTI measures evaluated in our study are markers of tissue diffusion, axonal integrity, and myelin sheath integrity [22] and, therefore, may be more sensitive to early demyelinating processes. It follows that the most likely underlying pathologic change in the WM would be demyelinating rather than axonal in nature. Indeed, in our study, the association with worse cognitive performance was driven primarily by worse RD, which is considered a better marker of myelin disruption [24] as opposed to LD

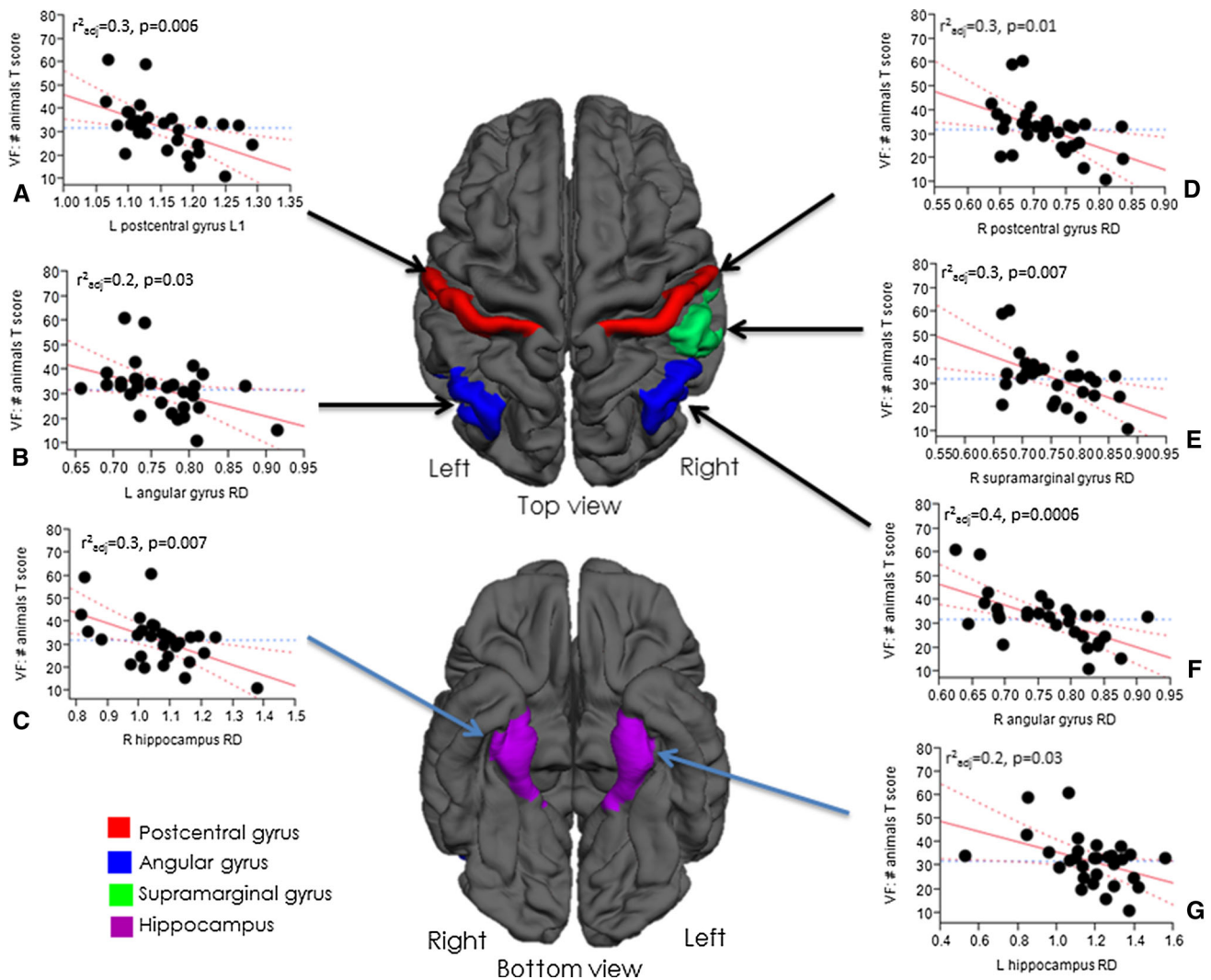


Fig. 1 Associations between white matter microstructural integrity and cognitive performance adjusting for age, HbA1c, mean BP, and the presence of WMHs in the MetS group. **a–g** Higher values in L post-central L1 (**a**), L angular gyrus-RD (**b**), R hippocampus RD (**c**), R post-central gyrus-RD (**d**), R supra-marginal gyrus-RD (**e**), R

angular gyrus-RD (**f**), and L hippocampus RD (**g**) are associated with lower performance in cognitive function. No significant associations were observed in the control group. *LD* axial diffusivity, *RD* radial diffusivity, *VF* verbal fluency

which is more likely to represent axonal damage [22, 24, 34] and was not markedly different between controls and MetS subjects.

Our results are in accordance with prior studies that have revealed an association between T2DM, WM microstructure disruption, and cognitive deficits [35–40]. MetS group had a higher global load of WMHs, which is considered a classic hallmark imaging sign of the cumulative effect of cardiovascular risk factors on the sub-cortical WM [41, 42], but neither global nor regional GM volumes were different between the two groups in our study, a difference which we might have been able to detect in a larger patient sample. The reasons for predilection of WM microstructural abnormalities are likely to stem from multiple mechanisms exerting their

effects on WM structure and integrity. T2DM has been associated with large and small vessel diseases, altered regional vasoreactivity [43], worse vasodilatation capacity [44], and reduced regional gray matter perfusion [45]. Given the fact that WM is more susceptible to ischemia compared with GM [46, 47], it is possible that a vascular mechanism plays a central WM pathology which is further supported by several studies demonstrating reduced perfusion and vasoreactivity in areas of leukoaraiosis [48–50]. Glucotoxicity associated with chronic hyperglycemia and glycemic variability may be another mechanism underlying WM and T2DM abnormalities [51].

The associations between regional DTI metrics and cognitive performance we report are statistically robust,

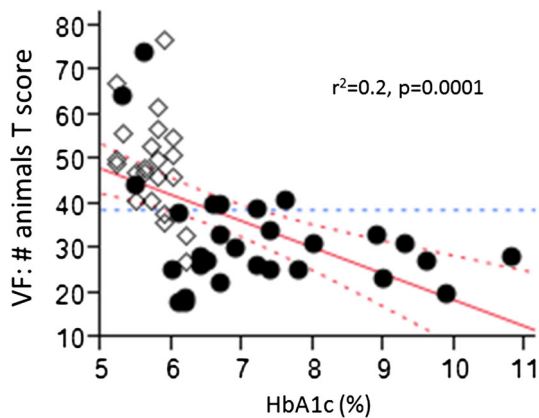


Fig. 2 Inverse association between HbA1c and VF: animals T score. Between the groups, a higher level of HbA1c at baseline is associated with a lower VF: animals T score. This supports the notion the glucose control in one of the factors that influence the most the cognitive performance in patients with MetS. *Circles* participants with MetS, *diamond* control participants. VF verbal fluency

they account for ~20–40 % of the variability in the cognitive performance after accounting for imbalances in cardiometabolic risk factors (Table 2). Given that our groups were otherwise well balanced with regard to age, education level, and gray matter volume, and that we excluded prior conditions, such as stroke, seizures, malignant tumors, alcohol abuse, recreational drug use, major surgery, there do not seem to be other obvious biologic factors that could explain these relationships. However, it should be noted that there are other aspects of cerebral WM network performance that our imaging methods might not have captured and which, if added, could shed more light into the pathophysiology of the process. Specifically, although WM structural alterations lead to impaired structural connectivity [9, 52], we have not accounted for this aspect of white matter network pathology. Accounting for functional connectivity could add another layer towards more elaborate characterization of WM network performance [53, 54].

Our study has some weaknesses, such as a relatively small sample, relatively well-controlled T2DM, hypertension, and other vascular risk factors that that might have underestimated their biologic effect. We did not have enough power to stratify patients into different degrees of MetS severity. Tractographic analysis, which could have potentially shed additional light on the effect of DM in specific WM tracts, was not performed. In addition, the cross-sectional nature of our study allows assumptions regarding associations, but it prohibits causal inferences to be made. It also prohibits us from making any assumptions regarding the trajectory of cognitive performance and potential for developing dementia in the future on individual patients.

Strengths of our study include prospective data collection, use of detailed and standardized cognitive test battery, and high-quality 3 T imaging with both global and regional metrics, which allowed detection of differences in small regions which would have otherwise been diluted if only global measurements were taken. Excluding subjects with strokes and dementia and the use of a relatively healthy control group allowed us to “isolate” the cognitive and anatomical effect of MetS and associated vascular risk factors as much as possible. In conclusion, our study provides evidence of an association between the presence of MetS and the development of abnormalities in the microstructural WM integrity.

In summary, we observed that subjects with MetS had impaired global and regional diffusivity parameters, which translated in a worse cognitive performance. These associations suggest that the cumulative effect of the cardiometabolic factors present in MetS may negatively affect the microstructural WM integrity early in the disease process, before macrostructural MRI changes become apparent. However, WMHs were not associated with worse learning parameters. It is important to point out that the previous studies have mostly found a link between these cardiometabolic factors and a decline in executive function [55], but our results add new evidence to the presence of underperformance in domains of verbal fluency and visuospatial memory as well. In our patient group, hyperglycemia seems to exert the most deleterious effect of all the components of MetS. DTI measures may provide a sensitive tool to detect abnormalities in the WM, before they manifest on anatomical MR scans as brain atrophy. Neuropsychological assessment of verbal fluency may be more sensitive to MetS-related cognitive disturbance than routine bedside clinical evaluation. A larger prospective study may be useful to further elucidate the role of DTI metrics as predictor of mid-life risk of MetS for subsequent gross anatomical MRI changes and cognitive decline.

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Compliance with ethical standards

Conflicts of interest Dr. Freddy Alfaro reports no disclosures. Dr. Vasileios-Arsenios Lioutas reports no disclosures. Dr. Daniela Pimentel reports no disclosures. Dr. Chen-Chih Chung reports no disclosures. Dr. Francisco Bedoya reports no disclosures. Dr. Woo-Kyoung Woo Ph.D. reports no disclosures. Dr. Vera Novak M.D. Ph.D. was funded by NIH-NIA 1R01- AG0287601A2, NIH-NIDDK 5R21 DK084463, NIH-NIDDK 1R01DK13902-01A1, American Diabetes Association, Clinical 1-03-CR-23 and 1-06-CR-25.

Ethical standards All subjects that met inclusion/exclusion criteria signed an Informed consent form (ICF) as approved by the Institutional review board (IRB) at Beth Israel Deaconess Medical Center.

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