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Does medial temporal lobe thickness mediate the association between risk factor burden and memory performance in middle-aged or older adults with metabolic syndrome?

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Abstract

Metabolic syndrome (MetS) is a cluster of cardiovascular and metabolic abnormalities that together may increase the risk of developing cognitive decline and dementia; however, the neural substrate is incompletely understood. We investigated cortical thickness in the medial temporal lobe (MTL), hippocampal volume, as well as relationships among metabolic risk factor burden, structure and memory performance. Path-analytic models were tested to explore the relations between MetS risk factor, structure and memory performance. Participants were 65 non-demented, middle-aged and older adults, 34 with and 31 without metabolic syndrome. We analyzed archival T1-weighted magnetic resonance imaging (MRI) acquired at 3T and Total Recall and Delayed Recall scores from the Brief Visuospatial Memory Test Revised (BVMT-R). Middle-aged adults with MetS showed less MTL thickness, particularly in entorhinal cortex; while older adults showed a trend for left hippocampal volume loss. Lower MTL thickness, particularly in entorhinal cortex, was associated with greater metabolic risk factor burden in middle-aged adults. In older adults, hippocampal volume was associated with Total Recall and Delayed Recall, while in middle-age entorhinal cortical thickness mediated the association between metabolic disease burden and episodic memory function. The differential findings in middle-aged and older adults with MetS contribute to an understanding of the relationships between metabolic syndrome, structural changes in the brain and increased risk for cognitive decline.

Keywords

Metabolic syndrome; medial temporal lobe; entorhinal cortical thickness; MRI; memory

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1. Introduction

The metabolic syndrome (MetS) is characterized by a cluster of inter-related and commonly co-occurring metabolic and cardiovascular risk factors. Individuals with MetS are twice as likely to develop cardiovascular disease over the next 5–10 years as individuals without MetS. In addition, those with MetS are at five times greater risk for type 2 diabetes mellitus (T2DM). The rising prevalence of MetS has rendered MetS both a clinical problem and a public health issue [1].

There is increasing evidence that metabolic markers increase the risk for cognitive decline and late life dementia. There are reports that MetS negatively affects memory, visuospatial abilities, executive functioning, processing speed, and general cognitive functioning [2]. MetS in both middle-aged and older adults has also been reported to be associated with risk for dementia, including Alzheimer's disease (AD) and vascular dementia [3, 4]. Studies of metabolic syndrome in midlife suggest that individual components of MetS may increase the risk for dementia in an additive fashion [3, 5]. Taken together, research on MetS and the cumulative effect of MetS components has increasingly reported that the presence of MetS as early as midlife can increase risk for future dementia, suggesting the important influence that metabolic syndrome has on susceptibility to neurodegenerative disease.

In investigations of MetS and structural brain changes, previous research demonstrated microstructural changes associated with MetS [6]. In line with neuropsychological reports of impaired performance on tasks that rely on frontal lobe function, Kaur et al. demonstrated that thinner cortical mantle in the inferior frontal ROI was associated with number of MetS risk factors [7]. Thus, there is evidence that MetS is associated with structural brain changes and that these changes are related to number of MetS risk factors.

Given the increasing evidence for an elevated risk for cognitive impairment in MetS and the wealth of evidence that AD-associated neurodegeneration begins in the medial temporal lobe (MTL), there have been surprisingly few investigations of the relationship between performance on memory measures and the integrity of MTL areas in individuals with metabolic syndrome. AD-associated neurodegeneration begins in the entorhinal/transentorhinal area and then progresses to other MTL structures, including the hippocampus [8]. Since MetS is associated with increased risk for AD, an investigation of how MetS related to MTL structures, and specifically entorhinal cortex and hippocampus, is particularly important. Song et al. examined cortical and subcortical thickness and volumes and reported reduced thickness in entorhinal cortex, but not other MTL regions. Potential relationships between structural compromise and memory performance were not investigated [9]. In healthy adults, it has been shown that entorhinal and hippocampal shrinkage predicts episodic memory performance [10, 11]. Thus, there is evidence of relationships between MetS and reduced entorhinal thickness, and between MTL changes and episodic memory performance in healthy adults, but past research has not adequately explored whether MTL structure mediates the relationship between MetS and episodic memory performance.

The purpose of the present study was to investigate structural differences in cortical thickness in brain regions known to be targeted early by neurodegenerative processes, i.e., the MTL, and specifically the entorhinal cortex and hippocampus, in middle-aged and older adults with MetS and the relationships among structure, MetS risk factors burden and memory performance. We made the following four hypotheses: (1) Due to the relationship between MetS and AD and evidence of structural brain abnormalities associated with MetS, it was hypothesized adults with MetS would have smaller estimates of cortical thickness in MTL structures and smaller volumes of the hippocampus relative to controls [3, 4, 9]; (2) Given previous findings showing relationship between cortical thickness and number of MetS risk factors, it was hypothesized cortical thickness in MTL and the entorhinal cortex, and hippocampal volume would be associated with the number of MetS risk factors [7]; (3) It was hypothesized cortical thickness in MTL structures and hippocampal volume would be associated with memory performance as these structures are critical to memory function [8]; and (4) Given previous evidence showing that MetS is associated with reduced entorhinal cortex [9] and other structural abnormalities [6], and evidence demonstrating relationships between MTL and memory decline, it was hypothesized that the relationship between MetS and memory performance would be mediated by structural changes in the MTL.

2. Materials and methods

2.1 Participants

Demographic data for the 65 participants (36 F, 29 M) are shown in Table 1. There were three study visits. Participants performed screening and clinical measures in the first, functional MRI (fMRI) neuroimaging in the second and cognitive testing in the third. Participants were screened for the following exclusionary criteria: left-handedness, neurological disorders, substance abuse, history of traumatic brain injury with at least five minutes loss of consciousness, and contraindications for MRI. Additionally, participants completed the Mini-Mental State Examination (MMSE) and adults > 60 completed the Dementia Rating Scale-2 (DRS-2) to screen for dementia. No older adults were excluded based on MMSE or DRS-2 scores. MetS status was determined using the International Diabetes Federation guidelines for clinical diagnosis of MetS [1]. Thus, MetS participants (n = 34) had at least three of the following: elevated waist circumference, elevated triglycerides, decreased high density lipoprotein (HDL) cholesterol levels (or treatment for HDL cholesterol), elevated systolic and/or diastolic blood pressure (or antihypertensive drug treatment), and elevated fasting glucose or T2DM diagnosis. Participants who did not meet the clinical criteria for MetS comprised the healthy control group (n =31). Participants gave informed consent and were compensated after each study visit. The study was conducted according to the principles of the Declaration of Helsinki and approved by the Institutional Review Boards at San Diego State University and the University of California, San Diego.

2.2 Clinical data

Clinical data acquired during the screening session included height, weight, waist circumference, and blood pressure. Height and weight were determined using a stadiometer and digital scale. Body mass index (BMI) was calculated by dividing the participant's weight (kilograms) by height (meters) squared. Waist circumference (centimeters) was

measured at the midpoint between the top of the hip bone (iliac crest) and the lowest point of the ribcage. Blood pressure was computed using the average of three seated measurements using an electronic blood pressure monitor. Participants completed a questionnaire to establish current medications being used to treat hypertension, dyslipidemia, or T2DM.

2.3 MRI

We analyzed archival high-resolution T1-weighted scans that had all been acquired on the same 3T GE Discovery MR750 scanner.

2.3.1 Scan Parameters—Thirty-nine participants were scanned using a high-resolution T1-weighted fast spoiled gradient (FSPGR) echo sequence with the following parameters: field of view (FOV) = 25.6 cm, slice thickness = 1.2 mm, resolution 1×1x1 mm^3, echo time (TE) = 30 ms, Locs per slab = 190, flip angle = 15°. The data for the remaining twenty-six participants were collected using a T1-weighted inversion recovery spoiled gradient (IR-SPGR) echo sequence with the following parameters: field of view (FOV) = 24 cm, slice thickness = 1.2 mm, resolution 0.9375×0.9375×1.2 mm^3, echo time (TE) = 3 ms, Locs per slab = 170, flip angle = 8°. The T1-weighted IR-SPGR sequence was collected using an image-based prospective motion correction technique (PROMO) in real time. Because fMRI upgraded the software for the T1 scans during the time periods of this study, scan parameters were different between participants. To control for this, type of scan was used as a covariate in analyses.

2.3.2 Image processing—T1-weighted structural scans were processed using the FreeSurfer image analysis suite, version 5.2.0 (http://surfer.nmr.mgh.harvard.edu). Standard FreeSurfer automated processing procedures were employed [12, 13]. Each subject's post-processing outputs were manually inspected for reconstruction accuracy in the Talairach transform, skull strip, white and pial surfaces, and segmentations. Cortical thickness regions of interest and volumetric estimates were extracted from automatic surface parcellation labels using the Desikan/Killiany Atlas [14]

2.4 Cognitive data

The Brief Visuospatial Memory Test-Revised (BVMT-R) [15], an episodic memory test that assesses learning and memory, was administered. We examined BVMT-R Total Recall (total score of three recall trials) and Delayed Recall because these have been reported to be effective in discriminating between middle-aged adults that remain stable or show cognitive decline and decline in episodic memory is an early cognitive change that precedes AD [16].

2.5 Statistical analysis

All statistical analyses, except for mediation analyses (Mplus), were performed using Statistical Package for the Social Sciences (SPSS, version 21). Nine participants did not undergo the cognitive testing, thus, analyses involving cognitive testing included 28 middle-aged (13 MetS) and 28 older adults (13 MetS). To preserve power, analyses not involving the cognitive data were performed on the full cohort: 34 middle-aged (18 MetS) and 31 older adults (16 MetS).

2.5.1 Demographics and clinical data—For both the middle-aged and older adult groups (N = 34, N = 31, respectively), two-tailed independent sample t-tests were conducted on age, education, MMSE, BMI, waist circumference, and systolic and diastolic blood pressure, and risk factor burden to examine group differences in demographics and clinical data. Additionally, chi-square analyses were used to examine differences in gender. Group differences in memory measures (BVMT-R Total Recall and Delayed Recall) were assessed in middle-aged and older adults using ANCOVA, controlling for age, education, and gender. Bonferroni-Holm correction was applied.

2.5.2 Group MRI analysis—To test our first hypothesis, Analysis of Covariance (ANCOVA) was performed to examine group differences (MetS vs. control) in global brain measures, cortical thickness of the MTL, the entorhinal cortex, and hippocampal volumes, in middle-aged and older adults separately. Estimates of cortical thickness of structures in the MTL and hippocampal volumes were extracted from automatic surface parcellation labels using the Desikan/Killiany Atlas. For each hemisphere, cortical thickness estimates of the MTL were calculated by computing the average thickness of MTL structures (entorhinal cortex, parahippocampal gyrus, temporal pole, fusiform gyrus). In addition, because of their importance in the early development of neuropathology in AD, we investigated entorhinal cortex thickness and hippocampal volume. Cortical thickness in bilateral areas (MTL) and hippocampal volumes were assessed for laterality effects using paired t-tests. Since there were significant differences in MTL thickness and hippocampal volume between the left and right hemispheres ($p < 0.01$), each hemisphere was examined separately in subsequent analyses. In all analyses, age, type of T1 scan, and gender were included as covariates. Additionally, estimated intracranial volume was controlled for in volumetric analyses. Groups were assessed for differences in nine structural measures: total MTL thickness, left/right MTL thickness, and individual MTL memory regions (total/left/right entorhinal cortical thickness, total/left/right hippocampal volume). Effect sizes (partial eta-squared, η_p^2) were calculated for all between-group comparisons. To correct for multiple comparisons, the Bonferonni-Holm correction was applied for each hemisphere separately. Unless otherwise specified, all MRI comparisons examined the same nine values described above.

2.5.3 Structural and clinical data relationships—To address the second hypothesis, two-tailed partial bivariate Pearson correlations between cortical thickness and volume estimates and metabolic risk factor burden were performed in middle-aged and older adults. Metabolic risk factor burden was determined by summing the total number of MetS criteria a participant met (range from) 0–4. We combined criteria for low HDL cholesterol and high triglyceride levels into one criterion (referred to as dyslipidemia). To assess the specificity of our findings, these relationships were also conducted for a control region in the occipital lobe (pericalcarine cortex) that is not known to be significantly affected by metabolic and cardiovascular factors or dementia. Age, type of T1 scan, and gender were controlled for in all partial correlation analyses. Bonferroni-Holm correction was applied.

2.5.4 Structural and memory performance relationships—To test the third hypothesis, the relationship between cortical thickness in the medial temporal region and

entorhinal cortex, hippocampal volume, and performance on memory measures (BVMT-R Total Recall and Delayed Recall) was investigated using two-tailed Pearson correlations, controlling for age, years of education, and T1 type, and gender in both middle-aged and older adult groups. The Bonferroni-Holm correction was applied.

2.5.5 Metabolic risk and cognitive data: Mediation analysis—To investigate the fourth hypothesis, path-analytic models specifying indirect relations from MetS risk factor to BVMT-R scores (Total Recall and Delayed Recall) via entorhinal cortex in middle-aged adults. Since entorhinal atrophy is known to precede hippocampal atrophy in neurodegenerative diseases like AD and MetS risk factors in mid-life are strong predictors of dementia, it was hypothesized a priori that entorhinal cortical thickness would mediate the relationship between MetS and memory in middle-aged adults.

2.5.6 Exploratory analyses

2.5.6.1 Relationships between hypertension and brain structure: Past research has shown hypertension, especially in middle age, to be associated with cognitive decline and structural brain changes [3]. Therefore, relationships between blood pressure (systolic and diastolic measurements) and cortical thickness in MTL areas and hippocampal volume were explored using regression analyses, covarying for age, gender, and T1 type. If significant relationships were found, the relevant blood pressure measurement was to be added as a covariate to the ANCOVA model to assess the contribution of blood pressure to group differences in brain structure.

2.5.6.2 Relationships between medication and brain structure: Due to the fact that MetS was defined by overt symptoms and/or use of symptom-reducing treatments, it is unclear whether medication use could account for the differences in brain structure seen in older adults with and without MetS. Therefore, the effect of medication treatment on cortical thickness differences was explored in two additional models in middle-aged and older adults. First, use of any medication for treatment of T2DM, hypertension, or dyslipidemia was coded and included as a variable of interest in ANCOVA models investigating structural group differences. Additionally, the effect of extensive medication use was evaluated by covering for the number of medication treatments (for T2DM, hypertension, dyslipidemia) for each participant.

3. Results

3.1 Demographics and clinical data

There were no significant differences between the MetS and control groups in age, years of education, or MMSE. As expected, there were significant group differences in BMI, waist circumference, metabolic risk factor burden, systolic and diastolic blood pressure readings in middle-aged adults. In older adults, there were significant group differences in BMI, waist circumference, metabolic risk factor burden, but not in blood pressure (Table 1). ANCOVA with age, education, and gender as covariates, detected no statistically significant differences between the MetS and control groups on the memory measures.

3.2 MRI analyses

3.2.1 Analyses of brain structure—ANCOVA analyses revealed important differences in cortical thickness between the MetS and control groups in medial temporal regions (Table 2). In middle-aged adults, relative to the control group, the MetS group had significantly smaller estimates of cortical thickness in bilateral MTL, including the entorhinal cortex. Additionally, middle-aged adults with MetS had significantly lower estimates of mean thickness in the left and right hemispheres. In older adults, there were no significant differences in cortical thickness in any medial temporal regions. However, older adults with MetS showed a trend toward smaller left hippocampal volumes compared to healthy older adults that did not reach significance after adjusting for multiple comparisons ($p = 0.046$). There were no group differences in any global volumetric or thickness measures in the older adults. Finally, there were no differences between MetS and control groups in the control region, the pericalcarine cortex ($p > 0.05$).

3.2.2 Relationships between metabolic risk factor burden and brain structure —Metabolic risk factor burden was negatively associated with cortical thickness in MTL and entorhinal cortex in middle-aged subjects (Table 3). Figure 1A–2A illustrate relationships between metabolic risk factor burden and cortical thickness in left MTL and in the left entorhinal cortex in middle-aged subjects. Correlations between number of risk factors and structural measures were not significant in older adults. Figure 3A illustrates the correlation between risk factor burden and hippocampal volume in older adults, p = 0.34. Analyses in the pericalcarine cortex (occipital control region) demonstrated no relationships between measures of metabolic risk factor burden and cortical thickness of this region ($p > 0.05$). Figures 1B–3B illustrate the MTL, entorhinal cortex and hippocampus in 3D.

3.2.3 Relationships between brain structure and memory performance—Correlations were performed between cortical thickness of MTL and entorhinal cortex and hippocampal volume and scores on the BVMT-R (Total Recall, Delayed Recall) (Table 4). In the older adults, total and left hippocampal volume was positively correlated with BVMT-R Total Recall and Delayed Recall. In middle-aged adults, relationships between left MTL and entorhinal thickness and BVMT-R Total Recall approached but did not reach significance after adjusting for multiple comparisons ($p = 0.032$, $p = 0.042$). Figures 1C–3C illustrate the data in middle-aged and older adults.

3.2.4 Relationships between metabolic risk factor burden and memory measures: Mediation analysis—As described above, previous literature has described relationships between number of MetS symptoms and brain structure, and MetS and worse cognition function, including memory, but few if any studies have tested whether the relationship between MetS and cognitive function is mediated by structural brain changes. We focused the analysis on the left entorhinal cortex because of the structural findings in the present study and because of its vulnerability to the very early degenerative changes in Alzheimer's disease. Thus, we examined the hypotheses that the relationship of MetS risk factor burden and memory performance is mediated by the cortical thickness of left entorhinal cortex in middle-aged. Path-analytic models specifying indirect relations from MetS risk factor to BVMT-R scores (Total Recall and Delayed Recall, separately) via

entorhinal cortex were tested to explore the relationships between MetS, structure and memory in middle age.

The first target model specified indirect relations from MetS risk factor to BVMT-R Total Recall score via left entorhinal cortex thickness as a mediating variable in middle-aged adults. The target model fit well statistically, $\chi^2(1, N=34) = 0.044$, $p = 0.833$, and descriptively (Comparative Fit Index (CFI) of 1.000 and Root Mean Square Error of Approximation (RMSEA) < 0.001. Both the effects from MetS risk factor to left entorhinal cortex thickness ($\beta = -0.419$, $p = 0.003$) and from left entorhinal cortex thickness to BVMT-R Total Recall score ($\beta = 0.403$, $p = 0.008$) were statistically significant.

The second target model specified indirect relations from MetS risk factor to BVMT-R Delayed Recall score via left entorhinal cortex thickness as a mediating variable in middle-aged adults. The target model fit well statistically [$\chi^2(1, N=34) = 0.077$, $p = 0.781$], and descriptively (CFI = 1.000, RMSEA < 0.001, and SRMR = 0.015). The effect from MetS risk factor to left entorhinal cortex thickness was statistically significant ($\beta = -0.382$, $p = 0.028$). The effect from left entorhinal cortex thickness to BVMT-R Delayed Recall score was not statistically significant ($\beta = 0.204$, $p = 0.161$).

3.3 Exploratory analyses

3.3.1 Exploratory analyses of hypertension and brain structure—Relationships between blood pressure (systolic and diastolic measurements) and brain structure were analyzed using regression analyses, covarying for age, gender, and T1 type. Systolic blood pressure was significantly associated with right MTL cortical thickness in middle-aged adults ($t = -2.198$, $p = 0.036$). However, when systolic blood pressure was added as covariate to the ANCOVA model analyzing between-group differences in right MTL cortical thickness, systolic blood pressure was no longer significant ($p = 0.350$) and the effect of MetS group was attenuated such that it was no longer significant ($p = 0.101$). In older adults, blood pressure measures were not associated with any structural measurements.

3.3.2 Exploratory analyses of medication and brain structure—In middle-age adults, cortical thickness differences in the left entorhinal cortex ($p = 0.047$) remained statistically significant after adding any medication use to the model. When assessing the effect of extensive medication use, group differences persisted in the left MTL ($p = 0.044$), and the left entorhinal cortex ($p = 0.018$) in middle-aged adults. There continued to be no significant structural differences in older adults after adjusting for medication use in either model.

4. Discussion

Hypothesis 1: Structural Differences in MetS

This study examined structural brain differences in middle-aged and older adults with MetS. Between-group analyses revealed that middle-aged adults with MetS had significantly smaller overall cortical thickness in the MTL, including the entorhinal cortex. In contrast, in the older adults, although there were trends toward a lower hippocampal volume, the MetS and control groups showed no significant differences in MTL thickness.

Middle age is increasingly being identified as a pivotal developmental period. Research suggests that lifestyle factors, especially during midlife, are associated with increased risk of dementia and AD [5]. The findings suggest that MetS differentially affects brain structure in middle age and older adulthood. It is not known why older adults with MetS did not show reduced cortical thickness compared to controls, as was seen in middle-age. Obesity and related MetS conditions rise with age with peak levels of MetS in the 6th decade for men and in the 7th decade for women and are associated with increased mortality [17], thus we speculate that a survivor effect may be present. Older adults with more chronic or severe MetS may have shorter life spans, be screened out for dementia or be unlikely to volunteer; e.g., due to cardiovascular disease. The data suggest the importance of longitudinal data that will further elucidate the association between metabolic syndrome, cortical thickness in MTL areas and memory measures through middle age and older adulthood. In addition, it will be important to measure the duration of the components of metabolic syndrome. Given that the earliest neuropathological changes in AD occur in entorhinal cortex, these data may be of use in understanding the influence of MetS on the development of cognitive decline and dementia.

We might speculate that middle-aged adults with MetS may demonstrate accelerated cerebral atrophy in MTL areas, which in turn may put this population at increased risk for cognitive decline and dementia. Though entorhinal atrophy is associated with typical aging and entorhinal atrophy in typically aging adults has been found to be predictive of memory performance [18], it is also an important feature of Alzheimer's disease. MRI studies in mild AD and AD populations have consistently reported volume loss in the entorhinal cortex [19], and longitudinal MRI studies of AD have found increased rates of atrophy in the entorhinal cortex relative to other brain structures [20]. In light of these findings, the results of the present study suggest that adults with metabolic syndrome may be susceptible to increased atrophy in brain regions that are consistently implicated early in neurodegenerative disease.

Hypothesis 2: Relationships between brain structure and number of MetS risk factors

Past research has shown several individual criteria of the MetS are associated with reduced cortical thickness or volumes. However, less is known about how number of individual vascular and metabolic risk factors, or cumulative MetS risk factors, affect brain structure. Yaffe (2007) showed that a composite measure of MetS is associated with greater risk for cognitive decline than any individual risk factor alone, except possibly insulin resistance [21]. In the present study, associations between cortical thickness in MTL regions and number of MetS risk factors were demonstrated in middle-aged adults. Cortical thickness of the control region was not associated with number of MetS risk factors, which suggests that effects of MetS on brain structure in the middle-aged are not indiscriminate, but rather are regionally specific.

In contrast to middle-aged adults, there were no significant relationships between MTL measures and risk factor burden in older adults. Recently, Tchistiakova et al. showed that older adults with both hypertension and T2DM had significantly less cortical thickness in the occipital lobe compared to older adults with hypertension alone [22]. Thus, there is some

evidence that older adults with multiple risk factors have less cortical thickness than adults with one risk factor, but not in the MTL. Future studies should build upon this line of inquiry to evaluate the contribution of cumulative vascular and metabolic risk factors to brain structure.

Hypothesis 3: Relationships between MTL structure and memory

A number of studies have suggested that MetS has a negative impact on memory processes [2]. Poor performance on the BVMT-R indicates difficulty in encoding and recalling new memories. In middle-aged adults, there were no significant associations between brain structure and memory. In older adults, hippocampal volumes were significantly correlated with both BVMT-R Total Recall and Delayed Recall. Overall, these findings suggest the hypothesis that the relationships between measures of memory function and MTL structure may progress over time in MetS. We might speculate that these differences in middle-aged and older adults reflect the same pattern as the development of pathology in AD which progresses from the transentorhinal/entorhinal area to hippocampus.

Hypothesis 4: Mediation Analyses

The present study was not designed to investigate the contribution of individual MetS criteria to differences in memory, but rather focused on the role of structural changes in mediating the relationship between MetS and memory in middle-aged adults. In middle-aged adults, left entorhinal cortical thickness mediated the relationship between metabolic risk factor burden and BVMT-R Total Recall. The results of the path analysis suggest that the relationship between cumulative MetS symptoms and episodic memory function is in part due to structural changes in the entorhinal cortex. It has repeatedly been shown that MetS is associated with poorer cognitive performance relative to healthy controls, but this is one of the first studies to show that poorer memory in MetS is related to an important structure implicated in neurodegenerative disease, the entorhinal cortex.

Exploratory analyses: Hypertension and brain structure

Hypertension is a known risk factor for cognitive impairment and dementia [3], thus, we also explored the relationships between blood pressure and MTL cortical thickness and hippocampal volume. Systolic and diastolic blood pressure were not significantly associated with structure of MTL memory regions, with the exception that systolic blood pressure was associated with right MTL cortical thickness in middle age. While hypertension has been shown to increase risk for cognitive impairment and dementia, these results suggest that hypertension alone cannot account for the differences seen in MTL structure. Further research is needed to fully investigate the potential influence of altered blood pressure on the integrity of temporal pathways. Recently, it has been shown that markers of arterial stiffness such as pulse-wave velocity, central blood pressure, and central pulse pressure were associated with MTL atrophy in older adults with memory complaints [23].

Exploratory analyses: Medication and cortical thickness

When we added use of any medication to the existing models, differences in cortical thickness remained between MetS and controls in the left entorhinal cortex. Further, adding

extensive medication use to the model did not alter the significant group differences in the left entorhinal cortex and the left MTL. Thus, accounting for medication use did not significantly alter the major findings related to cortical thickness in this study. In future studies, it would be of interest to include duration of medication use.

Strengths & Limitations

An important strength of this study is the use of cortical thickness as a measure of brain integrity. Cortical thickness has been shown to be regionally specific [12], and changes in cortical thickness are present in neurodegenerative diseases such as AD [24].

As with any study, the present study had limitations. The present study is cross-sectional. Nevertheless, it suggests relationships among risk factor burden, measures of MTL thickness and memory performance in middle-aged and older adults. The present results in a cross-sectional sample suggest the need for future studies to follow individuals with MetS longitudinally to further understand the degree to which structural changes in MTL mediate memory impairment and incipient dementia in MetS.

5. Conclusions

The present study is the first to demonstrate that not only do middle-aged adults with metabolic syndrome have smaller measures of cortical thickness compared to metabolically healthy adults in medial temporal regions, including the entorhinal cortex, but that these measures mediate the association between metabolic disease burden and performance on episodic memory function. The current study also suggests that MetS may differentially affect brain structure in middle age and older adulthood. Older adults with MetS did not show significantly decreased medial temporal cortical thickness, though there was a trend ($p < 0.046$) toward smaller hippocampal volumes relative to older controls. Given the established connections between medial temporal lobe atrophy and cognitive decline and dementia, our findings support the importance of longitudinal investigation of middle-aged and older adults with MetS who may be at increased risk for cognitive decline and pathological aging.

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Highlights

- The metabolic syndrome group had less cortical thickness in medial temporal lobe regions
- Cortical thickness differences were most pronounced in the left entorhinal cortex
- Cortical thickness mediated the association between risk factor burden and memory in middle age
- Differences in middle age and older adults contribute to an understanding of these relationships

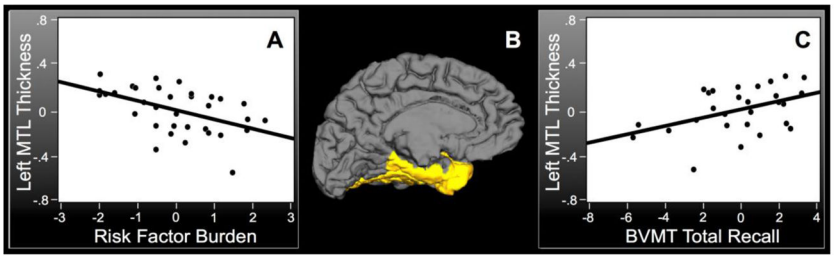

Fig. 1.

Scatterplots depicting partial correlations between residualized values of left medial temporal cortical thickness and metabolic risk factor score and memory performance in middle-aged adults; A) Relationship between left medial temporal cortical thickness and number of MetS risk factors (metabolic score) controlling for age, gender, and T1 type, r = −0.43, $p = 0.001$; B) Three dimensional representation of the left medial temporal lobe; C) Scatterplot showing data for left medial temporal cortical thickness and performance on BVMT-R Total Recall, controlling for age, gender, and T1 type, r =0.29, $p = 0.024$.

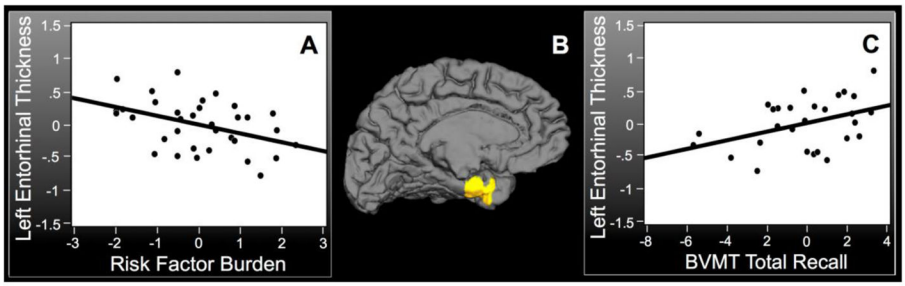

Fig. 2.

Scatterplots depicting partial correlations between residualized values of left entorhinal cortical thickness and metabolic risk factor score and memory performance in middle-aged adults; A) Relationship between left entorhinal cortical thickness and number of MetS risk factors (metabolic score), controlling for age, gender, and T1 type, r = −0.49, $p = 0.004$; B) Three dimensional representation of the left entorhinal cortex; C) Scatterplot showing data for left entorhinal thickness and performance on BVMT-R Total Recall, controlling for age, gender, and T1 type, r =0.44, $p = 0.028$.

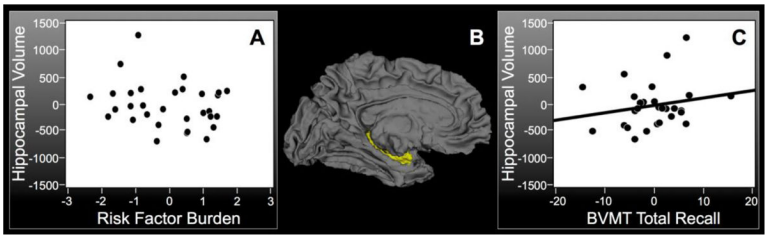

Fig. 3.

Scatterplots depicting partial correlations between residualized values of hippocampal volume and metabolic risk factor score and memory performance in older adults; A) Relationship between hippocampal volume and number of MetS risk factors (metabolic score), controlling for age, gender, and T1 type, r = 0.16, $p = 0.34$; B) Three dimensional representation of the hippocampus; C) Relationship between hippocampal volume and performance on BVMT-R Total Recall, controlling for age, gender, and T1 type, r =0.52, $p = 0.002$.

Table 1

Demographic and clinical data of MetS and control groups

Mid-Age Participants (N = 34)	**Control (N=16)**	**MetS (N=18)**		
	Mean (SD)		**t (χ^2)**	***P***
Age	49 (0.82)	50.72 (1.01)	−1.30	0.203
Education	15.13 (0.66)	14.61 (0.58)	0.59	0.56
Gender (% Male)	43.8	27.8	(0.95)	0.331
MMSE	29.31 (0.22)	29 (0.41)	0.65	0.523
BMI	25.22 (0.62)	40.29 (1.35)	−9.75	<0.001
Waist Circumference	91.69 (3.11)	126.27 (4.82)	−5.86	<0.001
Systolic BP	122.22 (4.45)	142.13 (2.96)	−3.80	0.001
Diastolic BP	75.52 (2.72)	85.6 (1.84)	−3.13	0.004
Risk Factor Burden	0.88 (0.18)	3.11 (0.18)	−8.79	<0.001
BVMT-R Total Recall	24.60 (4.39)	21.23 (8.37)	-	-
BVMT-R Delayed Recall	10.20 (1.42)	8.62 (3.28)	-	-
Older Participants (N=31)	Control (N=15)	MetS (N=16)		
	Mean (SD)		t (χ^2)	*P*
Age	70.4 (1.56)	68.25 (1.81)	0.90	0.378
Education	14.67 (0.67)	14.72 (0.62)	−0.06	0.955
Gender (% Male)	60.0	50.0	(0.31)	0.576
MMSE	28.53 (0.44)	28.69 (0.34)	−0.28	0.78
BMI	24.79 (0.72)	31.48 (1.09)	−5.05	<0.001
Waist Circumference	88.95 (2.08)	112.01 (2.86)	−6.45	<0.001
Systolic BP	139.51 (4.97)	138.63 (4.75)	0.13	0.9
Diastolic BP	72.01 (2.1)	77.17 (2.43)	−1.60	0.121
Risk Factor Burden	0.87 (0.13)	3.19 (0.14)	−12.17	<0.001
BVMT-R Total Recall	19.67 (6.30)	20.00 (7.88)	-	-
BVMT-R Delayed Recall	8.67 (2.72)	8.23 (3.03)	-	-

Table 2

Effect of MetS on MTL structures

Region of Interest	**Effect of MetS**		
Mid-Age Participants (N=34)			
	F	***p***	**η_p^2**
MTL Thickness	9.28	0.005	0.242
L MTL Thickness	8.42	0.007	0.225
Entorhinal Thickness	5.87	0.022	0.168
L Entorhinal Thickness	8.56	0.007	0.228
R MTL Thickness	7.14	0.012	0.198
Older Participants (N=31)			
NS			

Table 3

Correlations between risk factor burden and structural measures of medial temporal lobe

Region of Interest	**Corr. w/Risk Factor Burden**	
Mid-Age Participants (N=34)		
	R	***p***
MTL Thickness	−0.55	0.001
L MTL Thickness	−0.49	0.005
Entorhinal Cortex Thickness	−0.46	0.010
L Entorhinal Cortex Thickness	−0.43	0.017
R MTL Thickness	−0.53	0.002
Older Participants (N=31)		
NS		

Table 4

Correlations between structural measures of MTL/Memory areas and BVMT scores

Mid-Age Participants			
NS			
Older Participants			
Region of Interest	Measure	R	*p*
L Hippocampus Volume	BVMT-R Total Recall	0.51	0.013
	BVMT Delayed Recall	0.56	0.005
Hippocampus Total Volume	BVMT-R Total Recall	0.49	0.019
	BVMT Delayed Recall	0.54	0.007