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Research article

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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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.

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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.

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].

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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 $1 \times 1 \times 1$ 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 $0.9375 \times 0.9375 \times 1.2$ 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