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Posttraumatic Stress Disorder as a Catalyst for the Association Between Metabolic Syndrome and Reduced Cortical Thickness

Erika J. Wolf, Naomi Sadeh, Elizabeth C. Leritz, Mark W. Logue, Tawni B. Stoop, Regina McGlinchey, William Milberg, and Mark W. Miller

ABSTRACT

BACKGROUND: Metabolic syndrome (MetS), defined by a constellation of cardiometabolic pathologies, is highly prevalent among veterans, especially veterans with posttraumatic stress disorder (PTSD), and poses a major risk for adverse health outcomes, including neurodegeneration and mortality. Given this, we evaluated 1) the association between MetS and neural integrity, indexed by cortical thickness; 2) the relationship between PTSD and MetS; and 3) whether PTSD was associated with cortical thickness indirectly through MetS.

METHODS: The sample consisted of 346 U.S. military veterans (89.3% male; 71.4% white) who deployed to Iraq, Afghanistan, or both. Neuroimaging data were available for 274 participants.

RESULTS: In whole-brain analyses, MetS was negatively associated with cortical thickness in two left and four right hemisphere regions, as follows: bilateral temporal lobe, including temporal pole, fusiform gyrus, and insula, and extending into occipital cortex (left hemisphere) and orbitofrontal cortex (right hemisphere); bilateral precuneus, posterior cingulate, calcarine, and occipital-parietal cortex; and right rostral anterior cingulate cortex and central sulcus/postcentral gyrus. Path models showed that PTSD predicted MetS ($\beta = .19$, $p < .001$), which was associated with reduced cortical thickness ($\beta = -.29$ to $-.43$, all $p < .001$).

CONCLUSIONS: Results from this young veteran sample provide evidence that PTSD confers risk for cardiometabolic pathology and neurodegeneration and raise concern that this cohort may be aging prematurely and at risk for substantial medical and cognitive decline. This study highlights the need to identify the molecular mechanisms linking PTSD to MetS and effective interventions to reduce PTSD-related health comorbidities.

Keywords: Accelerated aging, Cortical thickness, Magnetic resonance imaging, Metabolic syndrome, Posttraumatic stress disorder, Structural equation modeling

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Metabolic syndrome (MetS) is a constellation of pathogenic cardiometabolic markers that collectively increase risk for cardiovascular disease (1,2), type 2 diabetes (2,3), cancer (4), cognitive decline (5,6), and death (1,7). MetS is defined by three or more of the following: obesity, high blood pressure, insulin resistance, and dyslipidemia (elevated triglycerides or low high-density lipoprotein) (8,9). Medical consensus is that when these symptoms co-occur, the health consequences are particularly profound (6,10). Stress, including psychological and traumatic stress (11–13), is thought to play a role in the pathogenesis and course of MetS (14–16), and various pathways have been implicated, including autonomic dysregulation and cardiovascular reactivity (13,17,18), hypothalamic-pituitary-adrenal axis dysregulation (13,16,17,19), oxidative stress (13,19–22), and immune system dysfunction (13,17–19).

Posttraumatic stress disorder (PTSD) has been linked to elevated risk for MetS (23–25). This disorder is defined by severe trauma exposure followed by reliving of the traumatic experience, avoidance of trauma-related stimuli, negative alterations in cognition and mood, and alterations in arousal and reactivity (26). It is prevalent among nearly one fourth of veterans of the conflicts in Iraq and Afghanistan (27) and poses a major public health concern (28) and financial burden (29). Chronic symptoms of PTSD, including emotional and physiologic reactivity, blunted positive affect, social isolation, sleep disturbance, hypervigilance, and startle, are thought to induce dysregulation in autonomic arousal (30), hypothalamic-pituitary-adrenal axis (31), and immune functioning (32,33) and may be associated with oxidative stress and premature cellular senescence (34–36). Two recent meta-analyses found that the prevalence of MetS in the presence of PTSD was 37%–39% (23,24), which was nearly double that of control subjects in the general population (23). Longitudinal studies also suggest that PTSD predicts increasing metabolic risk over time (37,38). Thus, MetS may be an important mechanism linking PTSD to a host of associated medical comorbidities, including cardiovascular disease (39–43), type 2 diabetes (44), cognitive decline (45), and premature death (35,39).

Features of MetS have also been shown to exert widespread effects on the structural integrity of the brain through reduced blood flow, which leads to suboptimal vessel perfusion and degeneration of brain tissue (46,47). Obesity is a strong predictor of decreased cortical thickness, an indicator of gray matter integrity (48,49), and this is most consistently found for temporal, frontal, and parietal regions (50–54). Blood pressure has been negatively associated with cortical thickness (55,56), as have glucose, insulin resistance, and type 2 diabetes (55,57–59). In contrast, cholesterol has shown less consistent patterns, with some studies supporting negative associations with cortical thickness (54) and others suggestive of positive associations (55,60). To our knowledge, only one prior study evaluated the combined effects of the full constellation of MetS markers on cortical thickness. Song *et al.* (61) found that a MetS diagnosis was associated with reduced cortical thickness in the left insular, superior parietal, postcentral, entorhinal, and right superior partial cortices in a sample of 86 participants (40 with MetS).

The primary aim of this study was to examine associations between PTSD, MetS, and neural integrity of the cortex in a cohort of veterans deployed to Iraq, Afghanistan, or both. We hypothesized that PTSD severity would be associated with greater MetS severity, which would be associated with reduced cortical thickness in temporal and frontal lobes.

METHODS AND MATERIALS

Participants

Participants were U.S. military veterans deployed to Iraq, Afghanistan, or both who underwent assessment at the Translational Research Center for TBI and Stress Disorders, a U.S. Department of Veterans Affairs Rehabilitation Research and Development Traumatic Brain Injury Center of Excellence at VA Boston Healthcare System. Exclusion criteria included history of seizures unrelated to head injury, neurologic illness, current psychotic or bipolar disorder, severe depression or anxiety, active homicidal or suicidal ideation with intent, cognitive disorder resulting from a general medical condition other than traumatic brain injury, and unstable psychological diagnosis that would interfere with accurate data collection. Additional magnetic resonance imaging (MRI) exclusion criteria included pregnancy and having a metal implant, shrapnel, aneurysm clip, or pacemaker. Measures related to MetS were available for 346 participants. Of these, 89.3% were men, and the mean age was 32.48 years (SD 8.95). Most of the sample (71.4%) reported their race as white; additional self-reported race and ethnicity was 15.6% Hispanic or Latino (Latina), 7.8% black, 1.7% Asian, and 1.2% American Indian. With respect to educational attainment, 34.4% of the sample had earned up to a high school degree or equivalent, and an additional 65.0% of the sample engaged in education beyond high school. Whole-brain cortical thickness data were available for a subset of 274 participants, none of whom had a history of moderate or severe traumatic brain injury. Demographic characteristics for this subgroup were nearly identical to the larger sample, as detailed in Supplementary Results and Supplemental Table S1.

Procedure

The protocol was approved by the relevant institutional review boards. Participants provided written informed consent and had early morning fasting blood samples drawn. Two standing and two seated blood pressure readings were taken at 1-minute intervals, and height, weight, and waist-to-hip ratio were measured. Blood samples were processed immediately and shipped the same day to a commercial laboratory for metabolic panels. A binary MetS variable was computed following the National Cholesterol Education Program Adult Treatment Panel III recommendations (Table 1) (9), which requires the presence of three or more MetS criteria for the diagnosis. Participants completed diagnostic interviews performed by a PhD-level clinician and underwent MRI scans.

MRI Acquisition and Processing

Structural imaging scans were completed in a 3-tesla Siemens MAGNETOM Tim Trio whole-body MRI scanner (Siemens Medical Solutions, Erlangen, Germany). Two T1-weighted anatomic scans (voxel size = 1 mm^3, repetition time = 2530 ms, echo time = 3.32 ms, field of view = 256 × 256, number of slices = 176) were performed and averaged to create a single high contrast-to-noise image. The FreeSurfer version 5.1 (available at http://surfer.nmr.mgh.harvard.edu/) morphometric pipeline was applied, including reconstruction of the cortical mantle and spatial smoothing of 20-mm full width at half maximum. Cortical surface models were manually checked slice by slice and edited for accuracy. Measurement of cortical thickness was calculated using procedures described previously (49,55,62). Additional MRI processing details are provided in the Supplement.

Measures

Diagnosis and symptom severity of PTSD was assessed with the Clinician-Administered PTSD Scale (CAPS) for DSM-IV (63), the gold standard PTSD structured diagnostic interview. The CAPS was administered for three time periods: past month (current PTSD), predeployment (if relevant predeployment trauma), and postdeployment (worst postdeployment symptoms). The frequency and intensity of symptoms were summed to form a severity score, and the highest value of these three assessments was used in analyses as an index of maximum lifetime PTSD severity. Psychiatric diagnoses were reviewed by an expert consensus team.

Data Analysis

Primary analyses modeled MetS using raw laboratory values and physiologic measurements, which were submitted to a confirmatory factor analysis (CFA) to form an overall index of the severity of MetS features (i.e., MetS severity). The CFA generates latent variables that capture the variance in common across multiple indicators to better reflect an underlying trait, such as an unobserved syndrome. Higher scores on the latent variable reflect greater pathology and co-occurrence of multiple MetS indicators; the CFA is preferable from a statistical and ecological validity standpoint to the use of arbitrary diagnostic thresholds. Our model included three lower-order factors to represent MetS components: latent