Metabolic Syndrome: Neurodegeneration and a Prelude to Dementia in Mexican-Americans

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Introduction

• Metabolic syndrome (MetS) is estimated to impact 35.4% of the US Hispanic population (Aguilar, 2015).

• Meeting the criteria for MetS has long been known to increases one's risk for developing cardiovascular disease and type II diabetes mellitus (T2DM).

• However, in recent years researchers have identified that these same criteria have negative effects on brain structure and function and are correlated with impaired executive function, processing speed, memory, and behavioral complications (Yates, 2012).

• Evidence also suggests that effects of MetS and neurocognitive dysfunction are bidirectional and complex, with genetic, environmental, and behavioral causes playing an important role (Biessels, 2014).

Abstract

The vast majority of neuroimaging studies have been carried out in homogenous populations comprised of Anglo-Americans, Northern Europeans, and Asians. Our study is one of the first to use an entirely Mexican-American cohort from the Genetics of Brain Structure data archive housed at the San Antonio Research Imaging Institute. We used voxel-based morphometry (VBM), a well-established structural MRI imaging analysis, to investigate regional gray matter atrophy differences between age- and sex-matched healthy controls (n = 108) and individuals meeting the International Diabetes Federation criteria for MetS (n = 108).

We found that there is a significant difference in gray matter density between individuals meeting the criteria for MetS and their age- and sex-matched healthy controls with statistically significant involvement in the following brain regions: bilateral caudate nuclei, orbitofrontal cortex, right parahippocampus/amygdala, right posterior insula, and posterior cerebellum.

The involvement of the posterior cerebellum, in particular, among the younger cohort suggest a pattern of neurodegeneration previously unreported in the metabolic syndrome literature, a pattern suggestive of the Cerebellar Cognitive Affective Syndrome that has been documented to negatively impact cognitive (specifically executive function) and emotional regulation.

Materials and Methods

1. Generate two age- and sex-matched cross-sectional groups from the G0BS dataset and divide them into MetS and healthy controls based on biometric scores.

2. Process T1-weighted brains using FSL software to extract gray matter volumes and transform brains into a standard space.

3. Use Voxel-Based Morphometry to contrast Healthy Controls > MetS (n = 208).

4. Use General Linear Modeling for multiple regressions to run a conditional Monte Carlo permutation test at 10,000 permutations to identify the most statistically robust regions of the brain impacted by MetS (p < 0.05).

5. Apply BrainMaps® Behavior, Task, and Disease Paradigm analysis to regional atrophy masks to determine the metabolic syndrome-associated effects on brain function and identify similar disease-related atrophy patterns.

6. Apply steps 3-5 on subjects below and above the median age (35.5 years). Young Healthy Controls > Young MetS (n = 104, mean age = 26.5 ± 4.6 years). Old Healthy Controls > Old MetS (n = 104, mean age = 48.1 ± 9.6 years)

Results

• There is a significant difference in gray matter volume between individuals meeting the criteria for MetS and their age- and sex-matched healthy controls counterparts.

• Atrophy is statistically significant across all subjects in the following brain regions: bilateral caudate nuclei, orbitofrontal cortex (nucleus accumbens), right posterior insula, and posterior cerebellum.

• Age effects play a significant role in the progression and diffusivity of gray matter regional atrophy (Fig. 5).

• Atrophied brain regions associated with MetS correspond to behaviors related to decision-making and reward perception an atrophy pattern closely resembling that of Huntington's and Alzheimer's Disease.

Conclusion

We report that MetS is associated with reduced gray matter volume, a finding that is amplified with age and begins in the posterior cerebellum. Gray matter regions negatively associated with MetS include those that are highly correlated with the behavior paradigms of reasoning and emotional valence. These regions and associated behaviors identified using the BrainMap meta-analytic tools recapitulate similar findings reported in the Cerebellar Cognitive Affective Syndrome.

Our findings thus propose the investigation of a novel hypothesis that early stages of cognitive decline associated with MetS have a unique etiology that differs from Alzheimer's disease, and other dementias.

References


