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Using the Schmahmann Syndrome Scale to Assess Cognitive Impairment in Young Adults with Metabolic Syndrome: A Hypothesis-Generating Report

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Abstract

The posterior cerebellum is the most significantly compromised brain structure in individuals with metabolic syndrome (MetS) (Kotkowski et al., 2019). In light of this, we hypothesized that cognitive decline reported in patients with MetS is likely related to posterior cerebellar atrophy. In this study, we performed a post-hoc analyses using T1-weighted magnetic resonance imaging (MRI), diffusion tensor imaging (DTI) in the form of voxel-wise tract-based spatial statistics

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(TBSS), biometric, and psychometric data from young participants with (n = 52, aged 18–35 years) and without MetS (n = 52, aged 18–35 years). To test the predictive value of components of the Schmahmann Syndrome scale (SSS), also known as the cerebellar cognitive affective syndrome scale, we used structural equation modeling to adapt available psychometric scores in our participant sample to the SSS and compare them to the composite score of all psychometric data available. Our key findings point to a statistically significant correlation between TBSS fractional anisotropy (FA) values from DTI and adapted SSS psychometric scores in individuals with MetS (r^2 = .139, 95% CI = 0.009, .345). This suggests that the SSS could be applied to assess cognitive and likely neuroanatomical effects associated with MetS. We strongly suggest that future work aimed at investigating the neurocognitive effects of MetS and related comorbidities (i.e. dyslipidemia, diabetes, obesity) would benefit from implementing and further exploring the validity of the SSS scale in this patient population.

Keywords

Metabolic Syndrome; Type 2 Diabetes Mellitus; Cerebellum; Voxel-Based Morphometry; Magnetic Resonance Imaging; Diffusion Tensor Imaging; Schmahmann's Syndrome; Cognitive Cerebellar Affective Syndrome

1. INTRODUCTION

Metabolic syndrome (MetS) is considered a major public health concern in the United States, with 34.7% of the American population meeting its clinical criteria (Aguilar et al., 2015). Though difficult to measure precisely, insulin resistance is widely accepted to be the underlying pathology driving the symptoms of MetS, comprised of: 1) elevated waist circumference, 2) hyperglycemia, 3) hypertension, 4) elevated triglycerides and 5) reduced HDL cholesterol (Grundy et al., 2005). In young adults in particular, it has been shown that executive function scores are negatively correlated with MetS status (Yates et al., 2012).

It has been hypothesized that diabetes-related cognitive decline is driven by insulin resistance in the brain's reward pathways (Lee et al., 2016), leptin resistance in the cerebellum (Berman et al., 2013), and white matter integrity loss, particularly in the cerebellar peduncles (Augustijn et al., 2017). Indeed, the cerebellum plays an important role in the regulation of speed, capacity, and consistency of cognitive processes much as it does with rate, force, rhythm, and accuracy of movements (Schmahmann, 2018). Lesion studies in the posterior cerebellum, as opposed to the anterior or the vermal regions, have demonstrated clinically relevant deficits in executive function, visual spatial performance, linguistic processing, and dysregulated affect (Stoodley et al., 2016). Moreover, the cognitive symptoms observed in patients with well-defined posterior cerebellar lesions have been collectively termed the Cerebellar Cognitive Affective Syndrome, or Schmahmann's Syndrome (Manto & Mariën, 2015).

A previous study conducted by our lab was the first to show that the cerebellumis the most strongly compromised region in neurophsychiatrically healthy participants with MetS. This region exhibits the largest correlation between gray matter volume (GMV) and MetS status. In the same study, meta-analytic behavioral domain and paradigm class analyses found that

the neural signature of MetS correlated strongly with reward perception, reasoning, and emotional valence. The surprising similarities between our objective meta-analysis and Schmahmann's Syndrome led us to hypothesize that a more focused analysis of MetS-associated cognitive decline using psychometric based on Schmahmann's Syndrome Scale is warranted. In this study, we restricted participant selection to a younger cohort to minimize confound effects including aging, medication use, variations in duration of metabolic syndrome, and MetS co-morbidities. We postulated that if negative cognitive effects are seen in a younger cohort of individuals with MetS, then a posterior cerebellar origin to such effects can be hypothesized for such psychometric variance. Furthermore, using an adapted Schmahmann Syndrome scale (SSS) generated from our available post-hoc primary data, we sought to evaluate whether Mets-associated gray-matter atrophy is significantly associated with cognitive impairments predicted by the SSS.

2. METHODS:

We conducted a post-hoc, cross-sectional analysis of young participants from the genetics of brain structure (GOBS) image archive and dataset, also used in our previous study (Kotkowski et al., 2019). From GOBS, we obtained T1-weighted brain images, MetS component values, diffusion tensor images, and psychometric scores of 104 young individuals (56% female; mean age = 25.6 ± 4.6 years, range = 18–35 years) (Winkler et al., 2010). Fifty-two metabolically healthy participants were age-, sex- and education-matched with 52 participants meeting the International Diabetes Federation's (IDF) criteria for MetS. All brain scans were obtained on a 3-Tesla scanner and processed using the FMRIB-Software Library's (FSL) optimized Voxel-Based Morphometry (VBM) protocol (Kotkowski et al., 2019) and DTI. The posterior cerebellar region of interest used in the correlation and regression analyses and reported as GMV values was also derived from Kotkowski et al.'s (2019) VBM analysis. The other regions of interest used in the analyses (hippocampus, anterior cerebellum, and whole brain, both gray and white matter) were derived from FSL atlases (Diedrichsen et al., 2009; Mori et al., 2005). Further image acquisition parameters and information about the GOBS archive can be found in the supplementary methods section.

Psychometric scores from the GOBS dataset were generated by a validated computerized neuropsychological assessment battery known as the South Texas Assessment of Neurocognition (STAN) (Glahn et al., 2010). We tested the SSS by matching similar subtests from STAN to mimic the subtests of the SSS as much as possible, further referred to as the "adapted" SSS (Hoche et al., 2018). Once subtests from STAN were aligned to the SSS, we used a confirmatory factor analysis, a feature of structural-equation modeling (SEM) (Supplementary Table 1) to derive a latent variable score (LVS) for each subject based on 9 subtests mirroring the SSS (Supplementary Table 2). Latent variable scores were corrected for measurement error, thereby increasing measurement precision. The confirmatory factor model exhibited excellent fit to the data with a comparative fit index (CFI) of .95 and root mean square error of approximation of .06 (Bollen et al., 1989; Kline et al., 2015) Coefficient Omega reliability (McDonald et al., 1999) of scores on the 9-subtest factor model was .89. Statistical power of each of the parameter estimates in the factor model was estimated using Markov chain Monte Carlo (MCMC) simulation within the

*M*plus structural equation modeling program. For all parameters in the model, power was observed as greater than or equal to .80. For a comparison, we also derived latent scores for each subject for the combined STAN battery of neuropsychological tests.

3. RESULTS:

Gray matter volume differences between a young cohort of metabolically healthy controls (HC) and MetS subjects were most pronounced in the posterior cerebellum (Cohen's D = −.66, CI = −1.06, −.26), (Table 1, Figure 1, Supplementary Figure 1, Supplementary Table 3) as compared to whole brain (Cohen's D = −.15, CI = −.54, .24) anterior cerebellar (Cohen's D = −.25, CI = −.64, −.14), and hippocampal GMV (Cohen's D = −.06, CI = −.32, .45). Importantly, GMV comparisons between MetS and HCs in the whole brain, anterior cerebellum, and hippocampus were not significant, supporting the specificity of posterior cerebellar gray matter findings in MetS. Tract-based spatial statistics (TBSS) analysis from diffusion tensor imaging (DTI) found multiple, widespread locations where fractional anisotropy (FA) showed significant white matter differences. For the purposes of this study, we reported the mean voxel-wise FA values for the whole brain that identified significant differences in white matter integrity between the two groups (Cohen's D = −.62, CI = −1.01, −.22) (Table 1, Figure 1, Supplementary Figure 2). Differences in psychometric scores between HC and MetS subjects were not significant for the adapted SSS (Cohen's D = −.31, CI = −.72, .09), and STAN scale (Cohen's D = −.27, CI = −.67, −.13).

Statistical comparisons between psychometric test scores and region-specific GMV using multiple regression were unimpressive. Individual latent scores and posterior cerebellar GMV values within the MetS cohort showed no significant correlations in both the adapted SSS (R^2 = .032, 95% CI = .000,.107) and STAN scale (R^2 = .020, 95% CI = .000,.106). However, the significance of the correlation between SSS and posterior cerebellar GMV corresponded to a p = 0.062, indicating that this trend might be worth exploring in future studies. Surprisingly, statistical comparisons between psychometric test scores and white matter integrity in the whole brain within the MetS cohort were statistically significant in the adapted SSS (R^2 = .139, 95% CI = .009, .345), but not the STAN scale (R^2 = .063, 95% CI = .000,.227). No differences were observed between psychometric tests within the HC cohorts in both posterior cerebellar GMV and whole brain white matter integrity.

4. DISCUSSION

Population-based studies - as opposed to disease-based studies - use unbiased sampling from the community, as represented in this study by the Genetics of Brain Structure (GOBS) cohort (Supplementary Methods Section; Kotkowski et al., 2019). This pilot analysis represents the first instance in which specific neuroanatomical findings from a community-based cohort were used to inform a best-practice approach for neuropsychological metrics in the context of chronic metabolic disease. The most robust results recapitulated earlier findings involving gray matter volume (Kotkowski et al., 2019) with new surprising findings in whole-brain white matter integrity (Table 1, Figure 1, Supplementary Figure 2). In short, significant differences exist in posterior cerebellar gray matter volume (GMV) between young individuals with metabolic syndrome (MetS) and healthy controls (HC). Those with

MetS have lower GMV than their age- and sex-matched HC counterparts. This finding also held true for whole-brain white matter integrity measured as fractional anisotropy (FA) values, whereby those with MetS had significantly lower FA values than HCs. Furthermore, we also found a significant positive correlation between FA values – but not GMV – and composite psychometric scores comprising the adapted Schmahmann Syndrome scale (SSS) in individuals with MetS.

Our findings suggest that that the underlying pathophysiology pertaining to our whole brain white matter integrity and posterior cerebellar gray matter findings may be connected. Previous studies have found that white matter integrity in the cerebellar peduncles are decreased in children with obesity. This difference from healthy controls likely results from alterations in axonal density, myelination, and/or fiber architecture related to dyslipidemia (Augustijn et al., 2017).

Functional relationships between our posterior cerebellar findings and functional connectivity are also likely. To further explore the connection between the neural signature of MetS region in the posterior cerebellum to the cerebral cortex, we ran a simple analysis to identify the percent overlap between our region of interest and functionally covarying cerebellar regions defined by Buckner et al. (2011) and Yeo et al. (2011). We found that networks 4 (ventral attention, aka salience processing and executive control) and 6 (frontoparietal) load most heavily on region of interest, comprising 32.2% and 31.1% respectively of the region's volume. Other notable networks include 3 (dorsal attention, aka goal-directed and stimulus-driven attention), 7 (default, aka mentalizing), and 2 (somatomotor), comprising 13.9%, 10.8%, and 8.8% of the region's volume respectively. Networks 1 (visual) and 5 (limbic) comprised the lowest percentage of our region's volume with 0.0% and 3.1% respectively (Supplementary Table 4). This may imply a hierarchical nature of MetS's effect on cognition, especially considering its varying relationship to specific functional networks.

This study represents a and hypothesis-generating preliminary analysis that used retrospective data to assess the feasibility of applying the Schmahmann Syndrome scale (SSS) as derived by Hoche et al. (2018) to test for cognitive changes in an increasingly common disease process - metabolic syndrome - known to implicate the posterior cerebellum. Our approach has wide implications in the study of disease processes exhibiting posterior cerebellum degeneration, especially in young people.

We acknowledge that the study had two key limitations: 1) the retrospective nature of the study and 2) the fact that we used SEM-based factor modeling to adapt the STAN neuropsychological tasks to fit the SSS (Supplementary Tables 1 & 2) instead of the discrete SSS. A further limitation was our sample size. A total of 104 subjects was not large enough to refute the null hypothesis using our adapted SSS in our posterior cerebellar gray matter hypothesis. The trends observed would require further validation analyses as well as a more robust prospective experimental undertaking.

In conclusion, we argue that our findings provide enough reason to continue exploring the relationship between posterior cerebellar gray matter volume, Schmahmann Syndrome and

SSS scores in the context of MetS, particularly in young adults. We also identified a novel connection between psychometric scores and white matter integrity in the whole brain that merit further study. Further, the SSS could become a useful neuropsychological tool to neuropsychologically monitor patients during the natural history of MetS and other comorbidities (i.e. dyslipidemia, diabetes, obesity, etc.) and/or assess the efficacy of therapeutics on cognition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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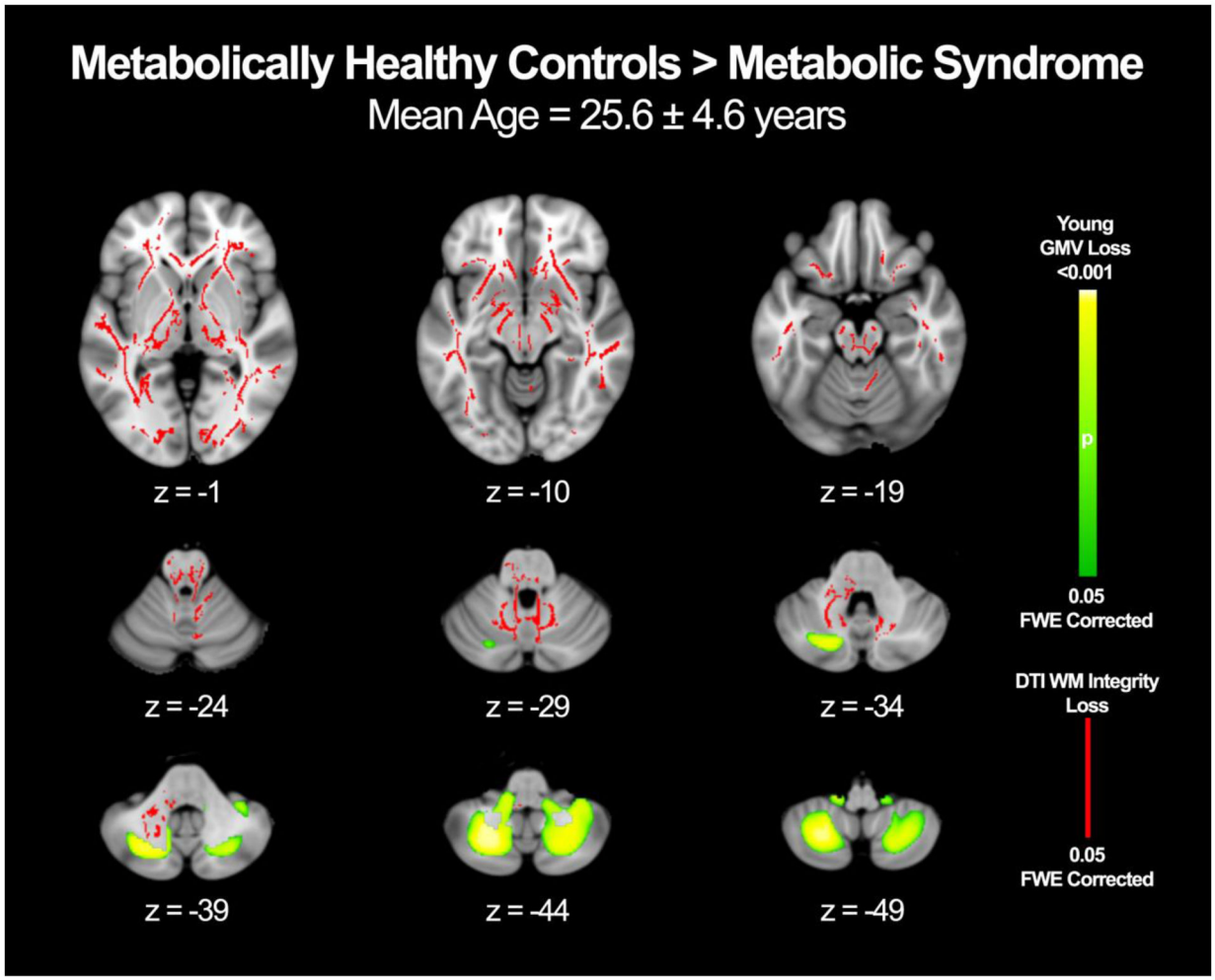

Figure 1:

Metabolically healthy control > Metabolic syndrome participants diffusion tensor imaging tract-based spatial statistics (DTI-TBSS) and gray matter volume (GMV) contrast (n = 104; 56% female; mean = 25.6 ± 4.6 years; range = 18 to 35 years) corrected for multiple comparisons across voxels using *randomise* and reporting a family-wise error rate of 0.05. A 3D representation of the implicated gray matter regions of the cerebellum with labeled anatomical sub-structures can be appreciated in Supplementary Figure 1. A coordinate-based representation of peak GMV loss foci can be appreciated in Supplementary Table 3.

Table 1:

Means, Correlations, and Bootstrapped Confidence Intervals

Region	Mean	95% CI	Cohen's D	95% CI
Posterior Cerebellar GMV				
Healthy Control	0.792	[0.752, 0.829]	−0.66*	[−1.06, −0.26]
Metabolic Syndrome	0.685	[0.638, 0.732]		
Hippocampal GMV				
Healthy Control	0.683	[0.669, 0.697]	0.06	[−0.32, 0.45]
Metabolic Syndrome	0.686	[0.672, 0.701]		
Anterior Cerebellar GMV				
Healthy Control	0.683	[0.690, 0.719]	−0.25	[−0.64, 0.14]
Metabolic Syndrome	0.686	[0.674, 0.706]		
Whole Brain DTI (FA values)				
Healthy Control	0.472	[0.467, 0.477]	−0.62*	[−1.01, −0.22]
Metabolic Syndrome	0.461	[0.457, 0.466]		
Whole Brain GMV				
Healthy Control	0.495	[0.490, 0.500]	−0.15	[−0.54, 0.24]
Metabolic Syndrome	0.493	[0.487, 0.498]		
Adapted SSS Composite Score				
Healthy Control	11.17	[10.38, 11.97]	−0.31	[−0.72, 0.09]
Metabolic Syndrome	10.27	[9.50, 11.07]		
STAN Scale Composite Score				
Healthy Control	11.00	[10.16, 11.86]	−0.27	[−0.67, 0.13]
Metabolic Syndrome	10.22	[9.51, 10.98]		
Correlation: Gray Matter Volume Variables in Posterior Cerebellum	**Psychometric Test**		**R^2**	**95% CI**
MetS vs Psychometrics	Adapted SSS		.032	[.000, .107]
	STAN Scale		.020	[.000, .106]
HC vs Psychometrics	Adapted SSS		.000	[.000, .101]
	STAN Scale		.002	[.000, .107]
Correlation: White Matter FA Variables in Whole Brain	**Psychometric Test**		**R^2**	**95% CI**
MetS vs Psychometrics	Adapted SSS		.139*	[.009, .345]
	STAN Scale		.063	[.000, .227]
HC vs Psychometrics	Adapted SSS		.022	[.000, .172]
	STAN Scale		.013	[.000, .137]

Abbreviations: SSS, Schmahmann Syndrome Scale; GMV, gray matter volume; DTI, diffusion tensor imaging; FA, fractional anisotropy; STAN; South Texas Assessment of Neurocognition; PC-GMV, posterior cerebellar gray matter volume; MetS, metabolic syndrome; HC, healthy controls; CI, confidence intervals.

*Statistically significant mean differences between healthy controls and MetS subjects ($p < 0.05$)