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Differential associations of metabolic risk factors on cortical thickness in metabolic syndrome

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ABSTRACT

Objective: Metabolic syndrome (MetS) refers to a cluster of risk factors for cardiovascular disease, including obesity, hypertension, dyslipidemia, and hyperglycemia. While sizable prior literature has examined associations between individual risk factors and quantitative measures of cortical thickness (CT), only very limited research has investigated such measures in MetS. Furthermore, the relative contributions of these risk factors to MetS-related effects on brain morphology have not yet been studied. The primary goal of this investigation was to examine how MetS may affect CT. A secondary goal was to explore the relative contributions of individual risk factors to regional alterations in CT, with the potential to identify risk factor combinations that may underlie structural changes.

Methods: Eighteen participants with MetS (mean age = 59.78 years) were age-matched with 18 healthy control participants (mean age = 60.50 years). CT measures were generated from T1-weighted images and groups were contrasted using whole-brain general linear modeling. A follow-up multivariate partial least squares correlation (PLS) analysis, including the full study sample with complete risk factor measurements (N = 53), was employed to examine which risk factors account for variance in group structural differences.

Results: Participants with MetS demonstrated significantly reduced CT in left hemisphere inferior parietal, rostral middle frontal, and lateral occipital clusters and in a right hemisphere precentral cluster. The PLS analysis revealed that waist circumference, high-density lipoprotein cholesterol (HDL-C), triglycerides, and glucose were significant contributors to reduced CT in these clusters. In contrast, diastolic blood pressure showed a significantly positive association with CT while systolic blood pressure did not emerge as a significant contributor. Age was not associated with CT.

Conclusion: These results indicate that MetS can be associated with regionally specific reductions in CT. Importantly, a novel link between a risk factor profile comprising indices of obesity, hyperglycemia, dyslipidemia and diastolic BP and localized alterations in CT emerged. While the pathophysiological mechanisms underlying these associations remain incompletely understood, these findings may be relevant for future investigations of MetS and might have implications for treatment approaches that focus on specific risk factor profiles with the aim to reduce negative consequences on the structural integrity of the brain.

1. Introduction

Metabolic syndrome (MetS) is defined as the constellation of three or more risk factors for atherosclerotic cardiovascular disease and type 2 diabetes mellitus (Eckel et al., 2005; Grundy, 2007). Component risk factors may include abdominal obesity, hypertension, dyslipidemia (low levels of high-density lipoprotein cholesterol (HDL-C) and high levels of triglycerides), and hyperglycemia (high levels of glucose)

Abbreviations: MetS, Metabolic Syndrome; HDL-C, high-density lipoprotein cholesterol; CT, cortical thickness; BP, blood pressure; PLS, partial least squares correlation; MRI, magnetic resonance imaging; VA, Veterans Administration Boston Healthcare System; GLM, general linear model; FDR, false discovery rate

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(Grundy, 2005). There is considerable evidence that the presence of MetS imparts augmented risk for stroke, cerebrovascular disease, cognitive decline, and dementia (Maruyama et al., 2009; Park and Kwon, 2008; Raffaitin et al., 2009; Wild et al., 2009; Yaffe, 2007; Yates et al., 2012). However, while the individual risk factors that comprise MetS have been linked to alterations in the structural integrity of the brain, less is known about the effects of MetS per se on brain structure (Friedman et al., 2014). Highly prevalent in the adult U.S. American population, with estimates ranging between 23% and 35%, MetS is projected to remain a serious public health concern (Aguilar et al., 2015; Beltrán-Sánchez et al., 2013; Grundy, 2008). Therefore, it is critical to understand how MetS affects brain structural integrity, particularly since its component risk factors can be modified via lifestyle changes and pharmaceutical treatment (Eckel et al., 2005; Grundy, 2007).

The component risk factors have been linked to brain tissue alterations in both white and gray matter (Friedman et al., 2014; Leritz et al., 2011; Salat et al., 2012; Tchistiakova et al., 2016; Veit et al., 2014; Vuorinen et al., 2013; Williams et al., 2013). As a sensitive marker of gray matter integrity, cortical thickness (CT) can provide information on cortical atrophy and has been employed in studies of cognitive function (Preul et al., 2005; Tchistiakova et al., 2016), aging (Fjell et al., 2009; Salat et al., 2004), neurodegenerative disease (Jacobs et al., 2014; Seo et al., 2012), small vessel disease (Preul et al., 2005; Reid et al., 2010), type 2 diabetes mellitus (Brundel et al., 2010; Tchistiakova et al., 2014), as well as in individual MetS risk factors (Alosco et al., 2014; Brundel et al., 2010; Hassenstab et al., 2012; Krishnadas et al., 2013; Leritz et al., 2011; Seo et al., 2012; van Velsen et al., 2013; Veit et al., 2014; Vuorinen et al., 2013). Using this metric to investigate neural health in generally healthy older adults, Leritz et al. (2011) reported significant negative associations between intra-individual variations in blood pressure (BP) factor scores (comprising systolic and diastolic BP) and quantitative measures of CT in frontal and temporal regions. In contrast, they also observed significant positive associations between a cholesterol factor (comprising total cholesterol and low-density lipoprotein cholesterol) and CT in widespread regions that prominently included frontal, parietal, and temporal cortices. Positive relationships in similar regions were reported for other lipid factors (Krishnadas et al., 2013), for visceral fat in adolescents (Saute et al., 2016), and for central adiposity in right posterior cingulate gyrus (Kaur et al., 2015a). Only a very limited number of studies have been published that have examined CT specifically in MetS cohorts, reporting regionally reduced CT in left insular, postcentral, and entorhinal and in bilateral superior parietal regions (Song et al., 2015). More recently, McIntosh et al. (2017) reported reduced CT of both hemispheres as well as in bilateral medial temporal lobe structures, which were chosen as regions of interest, relative to control groups. Similar observations have been made in related cohorts, for example, higher empirically-derived MetS severity scores (representing individual differences in MetS severity) were associated with reduced CT in orbitofrontal, temporal, cingulate, and occipital regions in U.S. military veterans (Wolf et al., 2016). Another study found that a greater number of MetS risk factors was associated with reduced CT in an inferior frontal region (Kaur et al., 2015b), although that relationship was mediated by a marker of inflammation. Furthermore, a greater number of vascular risk factors (represented as summative indices) was related to reduced CT measures in frontal and temporal regions in participants with mild cognitive impairment (Tchistiakova et al., 2016). Taken together, studies with both individual risk factors and with MetS suggest that vascular risk may affect CT in a regionally specific manner, including frontal, temporal and parietal regions. Given the sparse literature, it is currently not well understood in which way the component and co-occurring risk factors might contribute to these changes.

Composite measures like severity scores and risk factor counts, however, make it more difficult to assess which MetS components might be contributing more to altered gray matter integrity than others. Indeed, this is an important direction as empirical factor analytic studies have shown that MetS risk factors tend to cluster in specific patterns (Meigs, 2000; Wolf et al., 2016). For example, indices of insulin resistance (e.g., fasting blood insulin and glucose) often load on those factors that include measures of hyperglycemia, obesity, or dyslipidemia, and importantly, they load on more than one factor across studies (Gray et al., 1998; Hanley et al., 2002; Hanson et al., 2002; Meigs, 2000; Meigs et al., 1997; Sakkinen et al., 2000; Shen et al., 2003). Interestingly, BP most often emerges as a unique factor that only infrequently loads together with other variables (Hanley et al., 2002; Meigs, 2000; Sakkinen et al., 2000). That these studies yield more than one factor on which these variables converge suggests that there are separate disease mechanisms involved (Meigs, 2000). Examining whether there are particular patterns in which risk factors are related to alterations in CT might provide novel information on underlying pathophysiological processes in MetS. Accordingly, here we extend prior investigations and explore the relative contributions of component risk factors, in context of each other, to identify associations to CT in a MetS cohort.

The current cross-sectional study aimed to examine the integrity of cerebral gray matter, measured as CT across the entire cortical mantle, in participants with MetS. Based on prior findings in MetS and related cohorts and considerable literature examining the individual risk factors, we hypothesized that, overall, individuals with MetS would demonstrate primarily reduced CT in frontal, temporal, and parietal cortices relative to a control group (Kaur et al., 2015b; Leritz et al., 2011; McIntosh et al., 2017; Song et al., 2015; Wolf et al., 2016). However, since positive associations between CT and lipid factors and adiposity have been reported as well, regionally greater CT might also be identified (Kaur et al., 2015a; Krishnadas et al., 2013; Leritz et al., 2011; Saute et al., 2016). Consequently, a second aim was to use a partial least squares correlation (PLS) analysis to determine *which* risk factors may be most affiliated with patterns of CT in MetS-related brain regions. In doing so, we hope to shed light on whether there are particular combinations of risk factors underlying a MetS diagnosis that are particularly detrimental to cortical gray matter integrity.

2. Methods

2.1. Participants

Thirty-six participants of an initial sample of 59 were included in the group comparison to determine regions of MetS-related CT alterations and 53 participants were included in subsequent PLS analyses. Individuals were enrolled from direct clinic recruitment via the Veterans Administration Healthcare Services to target those at high risk for MetS, as well as through advertisement in the greater Boston, Massachusetts (USA) metropolitan area. Inclusion criteria required participants to be English speakers and between the ages of 30–90. Exclusion criteria encompassed significant medical disease (e.g., overt cardiovascular disease), neurological disorders (e.g., Parkinson's disease or dementia), prior major surgery (e.g., brain or cardiac surgery), head trauma (e.g., loss of consciousness for $>$ 30 min), history of severe or current psychiatric disorders (e.g., schizophrenia or major depressive disorder), history or current diagnosis of drug abuse or dependence, or any contraindication to magnetic resonance imaging (MRI).

From the initial sample of 59, four participants were excluded due to having insufficient physiological data to determine group assignment. The remaining cohort of 55 individuals was dichotomized into participants with and without MetS. While the HDL-C and waist circumference measurements were missing from two participants respectively, this did not affect group assignment as whether or not meeting MetS criteria could be determined from the remaining risk factor measures. Finally, 53 participants had a complete risk factor data set. MetS was defined as meeting thresholds for three or more of the following risk factors: 1) elevated waist circumference $\geq$ 102/88 cm or