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Differential associations between systemic markers of disease and cortical thickness in healthy middle-aged and older adults

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ABSTRACT

Aside from cortical damage associated with age, cerebrovascular and neurodegenerative diseases, it's an outstanding question if factors of global health, including normal variation in blood markers of metabolic and systemic function, may also be associated with individual variation in brain structure. This cross-sectional study included 138 individuals between 40 to 86 years old who were physically healthy and cognitively intact. Eleven markers (total cholesterol, HDL, LDL, triglycerides, insulin, fasting glucose, glycated hemoglobin, creatinine, blood urea nitrogen, albumin, total protein) and five derived indicators (estimated glomerular filtration rate, creatinine clearance rate, insulin-resistance, average glucose, and cholesterol/HDL ratio) were obtained from blood sampling of all participants. T1-weighted 3T MRI scans were used to evaluate gray matter cortical thickness. The markers were clustered into five factors, and factor scores were related to cortical thickness by general linear model. Two factors, one linked to insulin/metabolic health and the other to kidney function (KFF) showed regionally selective associations with cortical thickness including lateral and medial temporal, temporoparietal, and superior parietal regions for both factors and frontoparietal regions for KFF. An association between the increasing cholesterol and greater thickness in frontoparietal and occipital areas was also noted. Associations persisted independently of age, presence of cardiovascular risk factors and ApoE gene status. These findings may provide information on distinct mechanisms of inter-individual cortical variation as well as factors contributing to trajectories of cortical thinning with advancing age.

1. Introduction

Progressive age-related changes in gray matter volume and cortical thickness in healthy individuals follow a complex pattern and include noticeable changes in the prefrontal cortex, as well as lateral temporal lobes, medial parietal cortex, primary sensorimotor and visual cortices (Carmichael et al., 2013; Fjell et al., 2014; Salat et al., 2004). However, little is known on which factors may contribute to individual differences in brain structure prior to changes associated with senescence as well as what influence such factors might play in the trajectory of typical brain aging.

Outstanding attention has been drawn to identify structural brain changes that differentiate healthy aging from disease-related processes such as lesions of vascular origin and Alzheimer's disease (AD). Additionally, cardiovascular risk and disease (CVD) comprise a highly prevalent set of conditions in older adults that contribute to accelerated and altered trajectories of structural brain changes that are above and beyond those of typical aging and dementia and have been studied in detail (Gearing et al., 1995; Petrovitch et al., 2005; Sachdev et al., 2014). CVD can eventually modify brain structure through variable mechanisms, ranging from microvascular insults that present as white matter lesions to large infarcts (Gearing et al., 1995; Pantoni and Garcia, 1995; Sachdev et al., 2014).

It is now clear that health 'risk' states (states predictive of future

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disease) additionally influence brain structure even prior to a significant cardiovascular event. For example, reduction in gray matter volume is linked to hypertension, high cholesterol levels, poor peripheral glucose regulation and diabetes mellitus (Akintola et al., 2015; Meyer et al., 2000; Chen et al., 2006; Enzinger et al., 2005; Heijer et al., 2003; Jongen et al., 2007; Raz and Rodrigue, 2006; Schmidt et al., 2004; Tiehuis et al., 2008). Hippocampal and medial temporal atrophy has been shown in patients with diabetes and hypertension (Korf et al., 2005, 2007; Musen et al., 2006), and frontal and prefrontal cortices also seem to be particularly vulnerable to various CVD risk factors (Heijer et al., 2003; Raz et al., 2003, 2007; Reed et al., 2004). Taken together, these studies suggest that an overall higher risk of CVD is related to structural brain changes even without well-defined vascular lesions (Enzinger et al., 2005; Seshadri et al., 2004; Skoog et al., 1996). In older cognitively intact or near-normal participants, poorer kidney function was related to brain imaging measures of small vessel disease (Ikram et al., 2007), and lower brain volume has been related to insulin resistance and higher levels of visceral fat (Debette et al., 2010; Tan et al., 2011).

Aside from CVD, the study of the influence of other systemic diseases on individual variation and brain aging has been minimal, especially within normal limits of cognition. Particular regional relationships between higher blood pressure within or near “normal range” and reduced cortical thickness in prefrontal and temporal-parietal have been described (Leritz et al., 2011). It is noteworthy that such deleterious effects of systemic health on the brain do not seem to be restricted to disease or to individuals who fall into pre-clinical “abnormal ranges”.

Nevertheless, investigations linking variation in a diverse range of systemic health markers and variation in brain structure are lacking, particularly in the “normal range” spectrum of cognition and general health. We hypothesized that variation in systemic health would be associated with brain morphometry in an age-independent manner in individuals considered to be of typical health and aging. In this sense, “disease-free” or “disease-controlled” young and older brains could have some regional cortical differences according to each one's systemic health. Since healthier behavior and lower risks of CVD may be related to a lower development of cognitive impairment in older adults (Langa, 2015), this could contribute to our understanding of individual differences in brain aging within the wide range of “normality” prior and during typical senescence. Also, some of these various metabolic functions and organ systems may decline normally with aging and could contribute to alterations in brain structure.

The present work builds on one of our recent studies investigating associations between white matter integrity and a large variety of clinical laboratory parameters obtained from a fasting venous blood sample in a cohort of generally healthy and cognitively intact individuals in different stages of life, ranging from middle-aged to older individuals (Ryu et al., 2014, 2016). These clinical blood markers were grouped into five factors using factor analysis, which were related to insulin and metabolic regulation, peripheral glucose levels, kidney function, lipid regulation and blood protein levels. Given the differential physiological relevance of these markers, we hypothesized that we would see differential associations between blood factors and cortical thickness depending on the system. In the present cross-sectional study, we investigated the relationship between these five factors indicative of systemic health and cortical thickness in healthy young and older adults. Our main goal was to examine if and how common blood markers of general health relate to gray matter structural measures. Secondarily, we further defined the relationship between those factors and age and investigated possible impacts of cardiovascular risk factors (hypertension, type 2 diabetes and dyslipidemia) and Apolipoprotein E (ApoE) gene status on this relationship. Our findings suggest associations between cortical thickness and measures of lipid metabolic health and kidney function in the range of typical variation. These relationships tend to be present also prior to later aging. Our results provide novel insights into potential mechanisms influencing differential trajectories of the brain structure through the aging process.

2. Materials and methods

2.1. Study design and participants

A sample of 250 cognitively healthy middle-aged and older adults were recruited through the Massachusetts General Hospital, the local community, and local senior centers; these individuals form part of a longitudinal cohort to evaluate vascular contributions to brain aging. A total of 138 middle-aged and older adults (55 men/83 women) aged 40–86 years was selected for this cross-sectional study based on the availability of fasting venous blood sample and T1-weighted MRI data. All participants were physically healthy, cognitively intact, and literate with at least a high school education. Participants were excluded if they had major neurologic or psychiatric illnesses, history of stroke, significant head trauma, brain surgery or substance abuse, unstable medical illness, cancer within the nervous system or contraindications for an MRI scan. One hundred twenty-five participants were Caucasian (90.57%), 11 were African American (7.97%), and two were Asian.

Participants with controlled hypertension (HT), dyslipidemia (DLP), or type 2 diabetes (DM) were not excluded. Individuals with these characteristics represented 55.8% of the sample (total N=77; HT alone=18, DLP alone=23, DM=2; HT+DM=6, HT+DLP=14, DM +DLP=1, HT+DM+DLP=13).

The present work shares most of the participants with a prior investigating the effects of systemic health factors on white matter integrity with diffusion tensor imaging, with the exception of one subject lacking cortical thickness data (Ryu et al., 2016). Part of the sample (127 out of 138 individuals) also overlaps with a prior study investigating the impact of insulin resistance in white matter integrity (Ryu et al., 2014). There was no overlap in imaging methods analyses with any of our previous papers. The study was approved by the Partners Healthcare Internal Review Board (#2008P001486/MGH) and followed the Ethical Principles and Guidelines for the Protection of Human Subjects of Research, generally known as the Belmont Report. All participants provided written informed consent to participate in this research.

2.2. Clinical procedures

Assessments included ascertainment of medical history as well as general medical, physical, and neurologic examinations. Overnight fasting venous blood samples were collected on the day of the MRI session for estimation of 11 markers: total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride, fasting serum insulin, fasting glucose, glycosylated hemoglobin A1C (HbA1C), creatinine, blood urea nitrate (BUN), albumin, and total protein. Serum insulin was measured using electrochemiluminescence immunoassay (Mayo Medical Laboratories, Andover, MA). Five indicators of systemic health – homeostasis model assessment of insulin resistance (HOMA-IR), average glucose level, estimated glomerular filtration rate (eGFR), creatinine clearance (CCL) and cholesterol to HDL ratio (Chol/HDL ratio) – were calculated as per our previous study and will be further referenced in the text as blood markers (Ryu et al., 2016).

We also assessed the presence of the *epsilon* 4 allele of the Apolipoprotein E (ApoE E4), in a subset of the individuals. ApoE E4 is a well-know risk factor for the development of AD and an additional analysis of the relationship between cortical thickness and factors regarding the presence of this gene was performed. DNA for this analysis was extracted from frozen blood samples on the Autogen FlexStar instrument using Qiagen's FlexiGene chemistry. The DNA was quantified by Quant-iT PicoGreen assay (Invitrogen) and normalized to