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# Combined effects of type 2 diabetes and hypertension associated with cortical thinning and impaired cerebrovascular reactivity relative to hypertension alone in older adults

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ABSTRACT

*Objective:* Type 2 diabetes mellitus is characterized by metabolic dysregulation in the form of hyperglycemia and insulin resistance and can have a profound impact on brain structure and vasculature. The primary aim of this study was to identify brain regions where the combined effects of type 2 diabetes and hypertension on brain health exceed those of hypertension alone. A secondary objective was to test whether vascular impairment and structural brain measures in this population are associated with cognitive function.
*Research design and methods:* We enrolled 18 diabetic participants with hypertension (HTN + T2DM, 7 women, 71.8 ± 5.6 years) and 22 participants with hypertension only (HTN, 12 women, 73.4 ± 6.2 years). Cerebrovascular reactivity (CVR) was assessed using blood oxygenation level dependent (BOLD) MRI during successive breath holds. Gray matter structure was evaluated using cortical thickness (CThk) measures estimated from T1-weighted images. Analyses of cognitive and blood data were also performed.
*Results:* Compared to HTN, HTN + T2DM had decreased CVR and CThk in a spatially overlapping region of the right occipital lobe ($P < 0.025$); CVR group differences were more expansive and included bilateral occipito-parietal areas ($P < 0.025$). Whereas CVR showed no significant associations with measures of cognitive function ($P > 0.05$), CThk in the right lingual gyrus ROI and regions resulting from a vertex-wise analysis (including posterior cingulate, precuneus, superior and middle frontal, and middle and inferior temporal regions ($P < 0.025$) were associated with executive function.
*Conclusions:* Individuals with T2DM and HTN showed decreased CVR and CThk compared to age-matched HTN controls. This study identifies brain regions that are impacted by the combined effects of comorbid T2DM and HTN conditions, with new evidence that the corresponding cortical thinning may contribute to cognitive decline.


## 1. Introduction

Type 2 diabetes mellitus (T2DM) is among the most common conditions that affect individuals over the age of 65 years (Wu et al., 2013). Vascular complications associated with diabetes have profound effects not only on peripheral organs, but also on cerebral circulation. For instance, chronic hyperglycemia decreases elasticity of smooth muscle cells, reducing the ability of blood vessels to maintain sufficient blood and nutrient supply to brain tissue (Brownlee, 2005; Ergul, 2011). Vascular impairment increases the risk of neurological events, as seen by the increased risk of TIA and stroke by 2–5 fold in diabetic individuals (Baird et al., 2002; Kim et al., 2008). Along with vascular impairment, T2DM is associated with loss of gray and white matter tissue in excess of that seen in normal aging (Bresser et al., 2010; Last et al., 2007). Regions most susceptible to diabetic damage include prefrontal (Bruehl et al., 2009), hippocampal (Bruehl et al., 2009) and occipito-parietal areas (Last et al., 2007). These structural and vascular changes are

*Abbreviations:* 3DMPRAGE, three-dimensional magnetization-prepared rapid gradient-echo; BOLD, blood oxygenation level dependent imaging; BH, breath hold; CThk, cortical thickness; CVR, cerebrovascular reactivity; FLAIR, fluid attenuation inversion recovery; FLEX, fuzzy lesion extractor; HBA1C, hemoglobin A1C; HTN, hypertension; T2DM, type 2 diabetes mellitus; TICS, Telephone Interview for Cognitive Status; WMH, white matter hyperintensities.

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thought to contribute to increased impairment in speed of information processing, memory and executive function commonly reported in T2DM (Brands et al., 2007; Manschot et al., 2007).

There are still many gaps in our understanding on the impact of T2DM on the brain, one of which is the contribution of hypertension (HTN) that is comorbid in a reported 75% of individuals with T2DM (Colosia et al., 2013) as HTN itself contributes to brain vascular (Hajjar et al., 2010) and structural (Den Heijer et al., 2005) damages through mechanisms that both overlap with and are independent of T2DM (Meusel et al., 2012). A recent study demonstrated that individuals with T2DM have decreased brain tissue volumes and cerebrovascular reactivity (CVR) compared to healthy age-matched controls (Last et al., 2007). However, given the lack of control for the effects of HTN, the specific contributions of T2DM remain unclear. Poor hypertensive control was found to exacerbate macro- and micro-vascular T2DM complications (Turner et al., 1998), therefore, it is critical to not only establish individual effects of HTN and T2DM on the brain but to also address the combined effects of the two conditions. As a first step toward understanding the combined effects of T2DM and HTN, several studies contrasted normotensive and hypertensive diabetics and reported lower CVR (Last et al., 2007) and global volumetric measures (Schmidt et al., 2004) in those with both conditions, suggesting that HTN worsens vascular and structural abnormalities in the face of T2DM.

The current study attempts to advance this field of research, by specifically investigating the combined effects of HTN and T2DM (HTN + T2DM), relative to hypertension (HTN), as identified by measures of cortical gray matter thickness (CThk) and CVR. CThk has demonstrated high structural sensitivity in previous neuroimaging studies (Hutton et al., 2009; Pereira et al., 2011) and CVR is an established measure of vascular health (Riecker et al., 2003). Although controlled hypercapnia using $CO_2$ gas inhalation is closer to a gold standard, a breath hold technique for CVR assessment was selected for this study because of its ease of implementation (cognitive fMRI data were also collected and not reported in this manuscript).

We hypothesized that individuals with HTN + T2DM will show reduced regional CThk and reduced CVR relative to an HTN group. In addition, secondary objectives used measures of executive function, processing speed and memory to determine whether they have significant cognitive associations with CThk and CVR in this population (Nandipati et al., 2012; Takeuchi et al., 2012).

## 2. Methods

### 2.1. Study population

The study protocol was approved by Research Ethics Boards at Baycrest Centre and Sunnybrook Health Sciences Centre and experiments were conducted at Baycrest's Rotman Research Institute. Informed consent was obtained from all participants. Eighteen HTN + T2DM participants and twenty-two HTN participants were recruited through an internal participant database and via newspaper and community center advertisement. Participants completed a demographic and medical questionnaire via telephone. Those who scored within the dementia range on the Telephone Interview for Cognitive Status (TICS) (Brandt et al., 1988) or who self-reported having hepatic disease, recent coronary heart disease, other significant medical or psychiatric disorders affecting cognition (e.g., stroke, major depressive disorder), taking medications that act on the central nervous system (e.g. depression, sleep disorders, migraine headaches), hormone replacement therapy, major inflammatory disorders (e.g. arthritis), inflammatory bowel disease, rheumatological disorders, heart failure and chronic lung disease were excluded. Diabetic individuals were invited to participate as long as their disease, based on self report, did not include the following complications: retinopathy, nephropathy and neuropathy. Furthermore, controlling for diabetes through diet and/or hypoglycemic medication were inclusions, whereas use of insulin injections and T2DM diagnosis for less than 2 years were exclusions. Individuals recruited to the HTN group had to have fasting blood glucose levels less than 6.1 mmol/l on two consecutive testing days. Participants in both groups had a history of hypertension for at least 2 years, which was controlled by long-acting antihypertensive medications. Participants with MRI-incompatible metal implants, pacemakers and stents were excluded. On the first day of testing, participants provided a fasting blood sample and underwent neuropsychological testing to assess processing speed, memory and executive function. Blood pressure was measured during the same session using a blood pressure monitor (BpTRU Medical Devices), taken as the average of the last 5 of 6 readings, after participants had been sitting quietly for 5–10 min. During a second session, structural and functional brain MR imaging was performed. The time interval between neuropsychological testing and MRI was within 3 months (average 30.5 days; range 0 to 80 days) with the exception of one participant who was scanned after 372 days.

### 2.2. MRI

MR images were acquired on the 3 T Magnetom Trio Siemens system with 12-channel head coil. Anatomical imaging included T1-weighted three-dimensional magnetization-prepared rapid gradient-echo sequence (3DMPRAGE, TR/TE/TI = 2000/2.63/1100 ms, matrix = 256 × 192, FOV = 256 × 192 $mm^2$, slice thickness = 1 mm, number of slices = 160, flip angle = 9°, total duration = 6 min 30 s).

Cerebrovascular reactivity was measured as the change in blood oxygenation level dependent (BOLD) signal during a series of breath holds (BH) (TR/TE = 2000/30 ms, matrix = 64 × 64, FOV = 200 × 200 $mm^2$, slice thickness = 5 mm, number of slices = 32, flip angle = 90°, with 156 volumes, total duration = 5 min 20 s). The BH challenge consisted of six breath holds lasting 15 s each following 3 s expiration period with intermittent 30 s periods of normal breathing. The BH instructions were projected on the computer screen and included the start and end of the expiration period and the BH countdown. Fluid attenuation inversion recovery (FLAIR) images were also obtained to assess white matter hyperintensities (TR/TE/TI = 9000/96/2500 ms, matrix = 256 × 212, FOV = 224 × 186 $mm^2$, slice thickness = 5 mm, number of slices = 32, flip angle = 165°, total duration = 3 min 38 s).

### 2.3. Image analysis

Compliance with BH instructions was monitored using respiratory below traces recorded during the task. Participants with poor compliance (N = 2 for the HTN + T2DM and 1 for the HTN groups) were excluded from subsequent analysis. CVR analysis was conducted using tools available through FMRIB Software Library (FSL, version 4.1, http://fsl.fmrib.ox.ac.uk/). Preprocessing for BOLD images included: motion correction (Jenkinson et al., 2002), spatial smoothing with Gaussian kernel of 5 mm FWHM and high-pass temporal filtering with 100 s cutoff. Statistical analysis was carried out using a general linear model, i.e. a box-car paradigm was convolved with double-gamma hemodynamic response function to model the response to BH. Motion parameters were added as covariates of non-interest. A participant specific delay in hemodynamic response was estimated for each participant and incorporated into the model. Delay was computed by averaging the time difference between BOLD signal peaks in gray matter and the end of the corresponding BH. This procedure for estimating a response delay is valid for low to moderate hypercapnia conditions where signal increases are linear with blood $pCO_2$ (Tancredi and Hoge, 2013). To avoid bias related to initial compliance and baseline signal drift due to hyperventilation, for example, the first BH was discarded and analysis was performed on the remaining five BH trials. A cerebrovascular reactivity (%BOLD change) map for a representative HTN participant is shown in Fig. 1. CVR maps were generated for each participant and resampled to an average surface-based reference template. Surface-based analysis of the CVR data was chosen so as to match the geometry

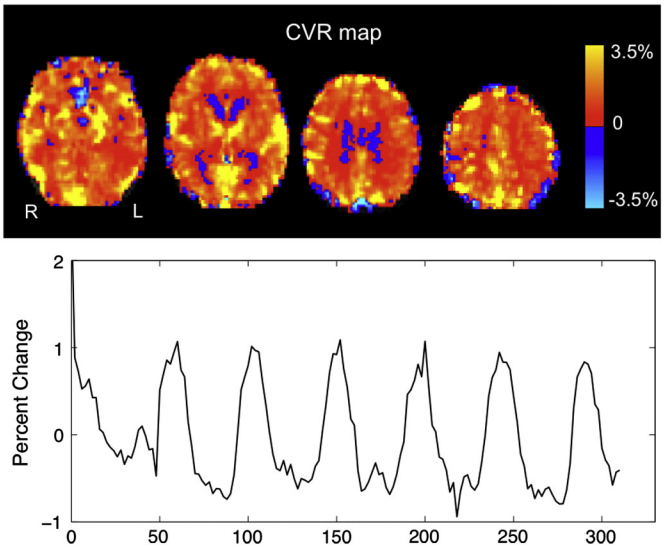


**Fig. 1.** Top: a CVR map for a representative HTN participant. Bottom: a mean BOLD time course for the same participant averaged across the entire brain.

for the CThk analysis (described below). It also has the advantages of improved inter-subject alignment and reduced partial volume influence when compared to the 3D analysis. Furthermore, a 2D representation of the cortex employed in the surface based analysis is thought to provide a more accurate anatomical description than a 3D volume-based analysis as it incorporates cortical folding information (Oosterhof et al., 2011; Tucholka et al., 2012).

Cortical surfaces for CVR registration and CThk measurements were generated for each participant using a freely available automated procedure in Freesurfer (V 5.1.0, http://surfer.nmr.mgh.harvard.edu/), described elsewhere (Fischl and Dale, 2000). Briefly: 1) high-resolution T1-weighted images were used to remove non-brain structures (Ségonne et al., 2004) and white matter was segmented, 2) gray matter/white matter boundary was covered with triangular tessellation and a deformation algorithm was applied to produce a final representation of the boundary between gray and white matter as well as the gray matter/CSF boundary, and 3) CThk was computed as the closest distance between gray/white and gray/CSF surfaces (Fischl and Dale, 2000). Cortical thickness maps and surface-registered CVR maps were computed for each participant separately and later registered to a spherical atlas, applying a 10 mm FWHM smoothing kernel, to facilitate inter-subject comparison (Fischl et al., 1999). FLAIR images were used in conjunction with in-house software, a fuzzy lesion extractor (FLEX) (Gibson et al., 2010) that is designed to segment white matter hyperintensities (WMH).

### 2.4. Correlation with cognitive scores

Three cognitive tests corresponding to cognitive domains implicated in previous research on T2DM (Nandipati et al., 2012; Takeuchi et al., 2012) were selected to examine the correlations with CVR and CThk. These measures included: 1) Trail Making Test A (time to complete) to assess processing speed, 2) California Verbal Learning Test (total number of words remembered over 5 trials) to examine memory function and 3) Wisconsin Card Sorting Test (number of categories achieved) to measure executive function.

### 2.5. Statistical analysis

Demographics, laboratory measurements and cognitive scores that were normally distributed were compared between the groups using an unpaired *t*-test in SPSS (v.21). A non-parametric Shapiro–Wilk test (SPSS) was used for group comparison of total cholesterol, C-reactive protein levels, BMI, WMH volumes, and executive scores that were not normally distributed. Unpaired two-group t-tests were performed on the cortical surface, i.e. vertex-wise, for CVR and CThk measures (mri_glmfit).

Per subject average CThk and CVR values were extracted from respective ROIs identified by the group comparison and examined for correlation with vascular risk factors and cognitive scores. A step-wise vascular risk factor linear regression (SPSS) was used to identify factors that contribute to observed CThk and CVR changes. Vascular risk factors included gender, age, total cholesterol, systolic blood pressure and WMH volume.

Associations between average CThk/CVR, extracted from respective ROIs, and cognitive scores were examined using partial correlation, controlling for the effects of age and education.

Finally, vertex-wise correlations of the brain measures were also conducted with the cognitive scores, with age and education and diagnosis as covariates. The group and regression analyses included correction for multiple comparisons using a Monte-Carlo simulation method (Hagler et al., 2006) with vertex P-value threshold of 0.05 and cluster-wise threshold of $P = 0.025$ ($P = 0.05/2$, to account for separate analysis of 2 hemispheres).

## 3. Results

### 3.1. Demographics

Demographic characteristics, laboratory measures, cognitive scores and WMH volumes were compared between HTN + T2DM and HTN groups (Table 1) and revealed that the groups were matched for age and sex. The HTN + T2DM group had higher hemoglobin A1C ($P < 0.0001$) and fasting blood glucose ($P < 0.0001$). Systolic blood pressure ($P = 0.02$), LDL cholesterol ($P < 0.0001$) and total cholesterol ($P < 0.0001$), on the other hand, were higher in the HTN group. Cognitive scores and WMH volumes were not significantly different between the two groups ($P > 0.2$).

### 3.2. Group differences in cerebrovascular reactivity and cortical thickness

CVR was significantly lower in the HTN + T2DM group in: 1) Bilateral — lingual gyrus, cuneus and superior parietal areas; 2) Right — lateral occipital, inferior parietal and precuneal regions; and 3) Left — pericalcarine cortex ($P < 0.025$), relative to the HTN group. Cortical thickness was lower in the HTN + T2DM group, compared to the HTN group, in the right lingual and fusiform gyri ($P < 0.025$). CVR and CThk results are both shown in Fig. 2, illustrating the spatially overlapping findings.

Post-hoc analyses of the vertex-wise correlations between CThk/CVR and HBA1C (a measure of glucose control), and between CThk/CVR and C-reactive protein level (a measure of inflammation), both commonly present at higher than normal levels in T2DM and HTN, showed no significance ($P > 0.05$, data not shown).

### 3.3. Correlation with vascular risk factors

Vascular risk factors could not explain between-subject differences in CThk and CVR, using functionally relevant ROIs (described in Section 3.2) and a step-wise linear regression ($P > 0.05$).

### 3.4. Correlation with cognitive scores

Average CThk in the right lingual gyrus ROI identified in group comparison was significantly associated with executive function ($P = 0.048$), after adjustment for age and education, whereas processing speed and attention were not ($P > 0.05$). No significant associations were found between average CVR and cognitive function ($P > 0.05$). Results of the vertex-wise analysis were similar to that of the ROI

**Table 1**
Participant demographics.

| | HTN group | HTN + T2DM group | Between-group comparison (P-value) |
|---|---|---|---|
| N | 22 | 18 | NS |
| Gender (women/men) | 12/10 | 8/10 | NS |
| Age (years) | 73.4 ± 6.2 | 71.8 ± 5.6 | NS |
| Diabetes duration (years) | NA | 10.9 ± 6.6 | NA |
| Hypertension duration (years) | 10.4 ± 6.9 | 10.3 ± 7.3 | NS |
| HBA1C % | 5.7 ± 0.3 | 6.9 ± 0.5 | <0.0001 |
| Fasting glucose (mmol/l) | 5.3 ± 0.3 | 7.2 ± 1.3 | <0.0001 |
| Fasting insulin (pmol/l) | 58.8 ± 19.3 | 65.0 ± 37.4 | NS |
| Systolic blood pressure (mm Hg) | 137.9 ± 15.8 | 125.1 ± 15.9 | 0.02 |
| Diastolic blood pressure (mm Hg) | 75.1 ± 10.7 | 70.6 ± 9.2 | NS |
| HDL (mmol/l) | 1.7 ± 0.4 | 1.5 ± 0.3 | NS |
| LDL (mmol/l) | 3.0 ± 1.0 | 1.9 ± 0.6 | <0.0001 |
| Total cholesterol (mmol/l) | 5.3 ± 1.1 | 3.9 ± 0.8 | <0.0001 |
| C-reactive protein (mmol/l) | 2.1 ± 1.4 | 3.6 ± 7.1 | NS |
| BMI | 26.3 ± 2.7 | 27.3 ± 4.0 | NS |
| WMH volume (cc) | 3.9 ± 7.4 | 2.8 ± 4.0 | NS |
| Cognitive scores | | | |
| Executive function (num. of categories) | 5.1 ± 1.4 | 4.4 ± 1.8 | NS |
| Processing speed (s) | 35.2 ± 9.9 | 35.5 ± 12.0 | NS |
| Memory function (num. of words) | 42.6 ± 10.2 | 41.8 ± 12.2 | NS |

Data are means ± SD unless specified otherwise.
Blood pressure measurements were not available for 3 participants (2 from HTN + T2DM and 1 from HTN groups).
Hemoglobin A1C (HbA1C) is an average measure of blood glucose levels over the prior 6–8 weeks.

analysis. Only executive function was significantly correlated with CThk ($P < 0.025$), after adjustment for age, education and diagnosis. Better executive function was associated with higher CThk in the: 1) bilateral — isthmus and posterior cingulate, precuneus, superior frontal, medial and lateral orbito-frontal regions; 2) left —middle and inferior temporal gyri and 3) right — rostral middle frontal areas (Fig. 3). CVR was not significantly associated with any of the cognitive scores ($P > 0.05$).

## 4. Discussion

This study demonstrates that the combination of T2DM and HTN is associated with decreased CThk and CVR in a spatially overlapping region of the occipital lobe, relative to a control group with HTN alone. CVR was significantly reduced in brain regions that extended beyond the occipital finding, which included bilateral occipito-parietal areas. Our secondary cognitive finding demonstrated that in individuals with systemic vascular conditions, such as T2DM and HTN, higher executive function is associated with preserved CThk in posterior cingulate, precuneus as well as temporal and frontal regions.

Diabetes leads to perfusion abnormalities, as reported in studies that compare patients and age-matched healthy controls (Kaplar et al., 2009; Last et al., 2007). Several studies also report reduced CVR compared to healthy individuals (Kaplar et al., 2009; Last et al., 2007). Yet in many instances, it is unclear whether T2DM per se, or commonly comorbid HTN, or a combined impact of the two, underscores these vascular changes. The results of the current study in older adults suggest

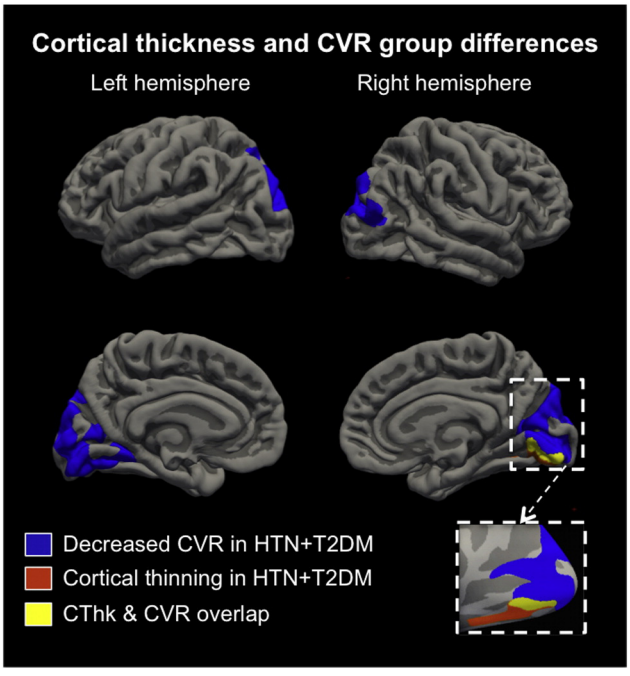


**Fig. 2.** Blue — regions of decreased CVR in HTN + T2DM group compared to HTN group; Orange — region of decreased CThk in HTN + T2DM group; Yellow — overlapping region of decreased CVR and CThk. Inset highlights region of CVR and CThk overlap which was overlaid on the inflated surface for enhanced visualization.

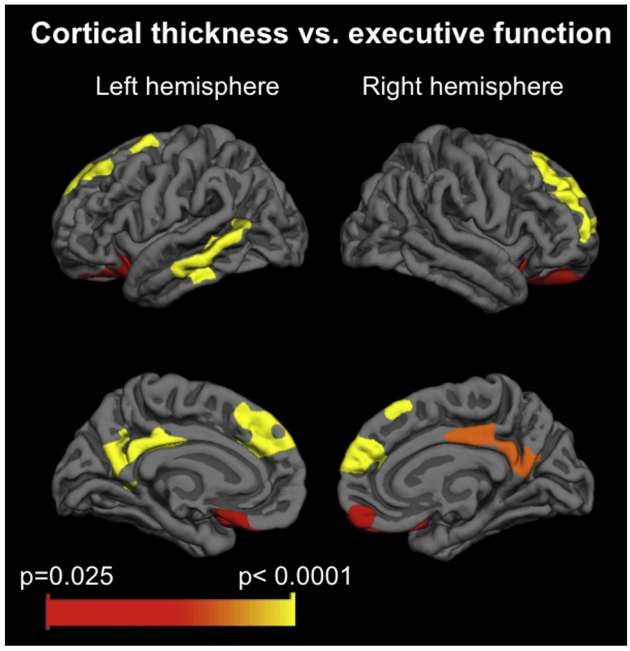


**Fig. 3.** Highlighted regions (red, orange and yellow) showed significant correlation between higher cortical thickness and better executive function. Executive function was assessed based on WCST score (number of categories achieved) and adjusted for age, education and diagnosis. Results are based on all participants included in the study ($N = 37$).

that the presence of both conditions, T2DM and HTN, contribute to cerebrovascular and structural abnormalities and that these changes are in excess of those apparent in older adults with HTN alone. Specifically, the combined effects of T2DM and HTN had a deleterious impact on both CVR and CThk in the occipito-parietal areas. Our CVR findings are regionally more localized compared to a previous report (Last et al., 2007), which may be due to our study design that included HTN in both study and control groups.

A regional decrease in CThk was detected in the right occipital region in the HTN + T2DM group compared to the HTN group. The region of reduced CThk was smaller in spatial extent but overlapping with the CVR results, which is a novel finding relative to the literature that has primarily focused on CThk in T2DM (Ajilore et al., 2010; Brundel et al., 2010; Chen et al., 2013; Leritz et al., 2011; Seo et al., 2012) and HTN separately (Seo et al., 2012; Vuorinen et al., 2013). A previous study involving older adults demonstrated that blood glucose levels and blood pressure were both associated with CThk thinning in occipital regions, among others (Leritz et al., 2011). These metrics of metabolic and hypertensive control identify regions that may be preferentially impacted by T2DM and HTN. The results of the current study are in agreement with these earlier findings and emphasize that occipital regions show greater impairment among adults with both T2DM and HTN conditions. This localized impact could be due to preferential impairment of posterior circulation. For example older adults with T2DM are more likely to develop infratentorial infarcts (Kameyama et al., 1994) and have a higher degree of vertebral stenosis (Iwase et al., 1998) than non-T2DM. Diabetes induced structural changes are often attributed to chronic exposure to hyperglycemia (Korf et al., 2006), inflammation (Novak et al., 2011), as well as direct and indirect effects of insulin dysregulation on the brain (Craft and Watson, 2004; Korf et al., 2006). Nevertheless, hyperglycemia as well as its underlying oxidative stress result in the release of proinflammatory cytokines that contribute to endothelial dysfunction (Monnier et al., 2006), reduce production of vasodilator nitric oxide (Brownlee, 2005; Kameyama et al., 1994) and increase concentration of vasoconstrictor endothelin-1 (Kalani, 2008). In case of the chronic exposure, such as in T2DM, these factors can lead to diminished vessel wall elasticity and impaired CVR (Last et al., 2007).

Cognitive impairment associated with T2DM (Brands et al., 2007; Manschot et al., 2007) and HTN (Dahle et al., 2009; Gifford et al., 2013) is well established, although it is still debated whether structural and/or vascular abnormalities play a mediating role. We observed a significant association between executive function and CThk in the superior and middle frontal gyri, middle and inferior temporal gyri and parietal regions. To our knowledge, this is the first study that examined the correlation between cognitive function and regional CThk focusing on individuals with T2DM and HTN. A study on a more general population, however, identified similar regions of association between CThk and executive function, namely in lateral prefrontal and parietal cortices (Burzynska et al., 2012). Others have also observed a negative correlation between subcortical atrophy and executive function and subcortical and cortical atrophy and information processing speed in individuals with T2DM (Manschot et al., 2006). Finally, in a recent large scale T2DM study, Moran et al. demonstrated that global gray matter atrophy can mediate differences in cognitive performance between individuals with and without T2DM, particularly in visuospatial memory and cognitive speed domains (Moran et al., 2013).

Although both T2DM and HTN are known to impact brain hemodynamics no studies to date reported on the correlation between regional CVR and cognitive function in this population. In the earlier T2DM studies global CVR (Brundel et al., 2012) and global baseline blood flow (CBF) (Brundel et al., 2012; Tiehuis et al., 2008) were examined for correlations with cognitive function. Similar to the results of the current study, no correlation was detected between CVR and cognition (Brundel et al., 2012), although CBF was associated with executive function (Brundel et al., 2012; Tiehuis et al., 2008) and processing speed (Brundel et al., 2012). Our findings in conjunction with this earlier work suggest that CBF but not CVR may act as a hemodynamic mediator on cognitive function in adults with T2DM and HTN, but further research is required.

In conclusion, our results demonstrate that CVR and CThk were able to provide independent and converging evidence of the adverse effects of combined T2DM and HTN, principally in the occipital lobes. Cortical thickness was correlated with executive function, which argues for the 'real world' relevance of cortical thinning in this population. As such it may serve as a useful imaging biomarker of cognitive decline in populations with commonly occurring HTN and T2DM.

## 5. Limitations

This study used a cross-sectional design, thus we can only speculate on the causal relationship between CVR and cortical thinning in the spatially overlapping occipital findings. Longitudinal studies are required to address a possible link between these two brain measures. The study was intentionally designed to exclude individuals with diabetes complications, such as retinopathy, neuropathy, and nephropathy, and study participants were in reasonably good diabetes control. Further study is needed to determine how these results extend to those with more severe or poorly controlled diabetes. For example, others have reported that retinopathy associates with greater CVR impairment (Last et al., 2007).

Other limitations include the lack of information on hematocrit and blood $CO_2$ levels during the CVR experiment that may contribute to individual CVR differences. Angiographic MR data were not available to judge steno-occlusion of major vessels, which could also influence CVR. Our CVR findings were largely confined to occipital regions, whose functional roles include processing visual information. Given that the breath hold task instructions were displayed on the screen, it is possible that some of the group differences may be attributed to neuronal activation differences. Structural changes were however detected in the same region, which would suggest that there is a structural or neurovascular basis for the differences observed between HTN + T2DM and HTN groups.

Higher blood pressure and cholesterols levels were observed in the control HTN-only group. Although unexpected, this might be explained by HTN + T2DM group selection criteria, with many participants controlling their diabetes through diet and exercise and the fact that they were in reasonably good metabolic control.

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## References

Ajilore, O., Narr, K., Rosenthal, J., et al., 2010. Regional cortical gray matter thickness differences associated with type 2 diabetes and major depression. Psychiatry Res. Neuroimaging 184 (2), 63–70.
Baird, T.A., Parsons, M.W., Barber, P.A., et al., 2002. The influence of diabetes mellitus and hyperglycaemia on stroke incidence and outcome. J. Clin. Neurosci. 9 (6), 618–626.
Brands, A.M.A., Biessels, G.J., Kappelle, L.J., et al., 2007. Cognitive functioning and brain MRI in patients with type 1 and type 2 diabetes mellitus: a comparative study. Dement. Geriatr. Cogn. Disord. 23 (5), 343–350.
Brandt, J., Spencer, M., Folstein, M., 1988. The telephone interview for cognitive status. Neuropsychiatry Neuropsychol. Behav. Neurol. 1 (2), 111–117.
Bresser, J., Tiehuis, A., van den Berg, E., et al., 2010. Progression of cerebral atrophy and white matter hyperintensities in patients with type 2 diabetes. Diabetes Care 33 (6), 1309–1314.
Brownlee, M., 2005. The pathobiology of diabetic complications — a unifying mechanism. Diabetes 54 (6), 1615–1625.
Bruehl, H., Wolf, O.T., Sweat, V., Tirsi, A., Richardson, S., Convit, A., 2009. Modifiers of cognitive function and brain structure in middle-aged and elderly individuals with type 2 diabetes mellitus. Brain Res. 1280, 186–194.
Brundel, M., Van Den Heuvel, M., De Bresser, J., Kappelle, L.J., Biessels, G.J., 2010. Cerebral cortical thickness in patients with type 2 diabetes. J. Neurol. Sci. 299 (1–2), 126–130.

Brundel, M., Van Den Berg, E., Reijmer, Y.D., De Bresser, J., Kappelle, L.J., Biessels, G.J., 2012. Cerebral haemodynamics, cognition and brain volumes in patients with type 2 diabetes. J. Diabetes Complications 26 (3), 205–209.
Burzynska, A.Z., Nagel, I.E., Preuschhof, C., et al., 2012. Cortical thickness is linked to executive functioning in adulthood and aging. Hum. Brain Mapp. 33 (7), 1607–1620.
Chen, Z.-, Li, J.-, Sun, J., Ma, L., 2013. Study of cortical thinning in the patients with type 2 diabetes mellitus and the recovering effect of the insuline therapy. Nat. Med. J. China 93 (17), 1313–1317.
Colosia, A.D., Palencia, R., Khan, S., 2013. Prevalence of hypertension and obesity in patients with type 2 diabetes mellitus in observational studies: a systematic literature review. Diabetes Metab. Syndr. Obes. 6, 327–338.
Craft, S., Watson, G.S., 2004. Insulin and neurodegenerative disease: shared and specific mechanisms. Lancet Neurol. 3 (3), 169–178.
Dahle, C.L., Jacobs, B.S., Raz, N., 2009. Aging, vascular risk, and cognition: blood glucose, pulse pressure, and cognitive performance in healthy adults. Psychol. Aging 24 (1), 154–162.
Den Heijer, T., Launer, L.J., Prins, N.D., et al., 2005. Association between blood pressure, white matter lesions, and atrophy of the medial temporal lobe. Neurology 64 (2), 263–267.
Ergul, A., 2011. Endothelin-1 and diabetic complications: focus on the vasculature. Pharmacol. Res. 63 (6), 477–482.
Fischl, B., Dale, A.M., 2000. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc. Natl. Acad. Sci. U. S. A. 97 (20), 11050–11055.
Fischl, B., Sereno, M.I., Tootell, R.B.H., Dale, A.M., 1999. High-resolution intersubject averaging and a coordinate system for the cortical surface. Hum. Brain Mapp. 8 (4), 272–284.
Gibson, E., Gao, F., Black, S.E., Lobaugh, N.J., 2010. Automatic segmentation of white matter hyperintensities in the elderly using FLAIR images at 3 T. J. Magn. Reson. Imaging 31 (6), 1311–1322.
Gifford, K.A., Badaracco, M., Liu, D., et al., 2013. Blood pressure and cognition among older adults: a meta-analysis. Arch. Clin. Neuropsychol. 28 (7), 649–664.
Hagler Jr., D.J., Saygin, A.P., Sereno, M.I., 2006. Smoothing and cluster thresholding for cortical surface-based group analysis of fMRI data. Neuroimage 33 (4), 1093–1103.
Hajjar, I., Zhao, P., Alsop, D., Novak, V., 2010. Hypertension and cerebral vasoreactivity: a continuous arterial spin labeling magnetic resonance imaging study. Hypertension 56 (5), 859–864.
Hutton, C., Draganski, B., Ashburner, J., Weiskopf, N., 2009. A comparison between voxel-based cortical thickness and voxel-based morphometry in normal aging. Neuroimage 48 (2), 371–380.
Iwase, M., Yamamoto, M., Yoshinari, M., Ibayashi, S., Fujishima, M., 1998. Stroke topography in diabetic and nondiabetic patients by magnetic resonance imaging. Diabetes Res. Clin. Pract. 42 (2), 109–116.
Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17 (2), 825–841.
Kalani, M., 2008. The importance of endothelin-I for microvascular dysfunction in diabetes. Vasc. Health Risk Manag. 4 (5), 1061–1068.
Kameyama, M., Fushimi, H., Udaka, F., 1994. Diabetes mellitus and cerebral vascular disease. Diabetes Res. Clin. Pract. 24, S205–S208 (Suppl.).
Kaplar, M., Paragh, G., Erdei, A., et al., 2009. Changes in cerebral blood flow detected by SPECT in type 1 and type 2 diabetic patients. J. Nucl. Med. 50 (12), 1993–1998.
Kim, B.J., Lee, S.-, Kang, B.S., Yoon, B.-., J-, Roh, 2008. Diabetes increases large artery diseases, but not small artery diseases in the brain. J. Neurol. 255 (8), 1176–1181.
Korf, E.S.C., White, L.R., Scheltens, P.H., Launer, L.J., 2006. Brain aging in very old men with type 2 diabetes: the Honolulu–Asia aging study. Diabetes Care 29 (10), 2268–2274.
Last, D., Alsop, D., Abduljalil, A., et al., 2007. Global and regional effects of type 2 diabetes on brain tissue volumes and cerebral vasoreactivity. Diabetes Care 30 (5), 1193–1199.
Leritz, E.C., Salat, D.H., Williams, V.J., et al., 2011. Thickness of the human cerebral cortex is associated with metrics of cerebrovascular health in a normative sample of community dwelling older adults. Neuroimage 54 (4), 2659–2671.
Manschot, S.M., Brands, A.M.A., Van Der Grond, J., et al., 2006. Brain magnetic resonance imaging correlates of impaired cognition in patients with type 2 diabetes. Diabetes 55 (4), 1106–1113.
Manschot, S.M., Biessels, G.J., De Valk, H., et al., 2007. Metabolic and vascular determinants of impaired cognitive performance and abnormalities on brain magnetic resonance imaging in patients with type 2 diabetes. Diabetologia 50 (11), 2388–2397.
Meusel, L., Tchistiakova, E., Yuen, W., MacIntosh, B., Anderson, N., Greenwood, C., 2012. Vascular and metabolic contributions to cognitive decline and dementia risk in older adults with type 2 diabetes. J. Curr. Clil Care 2 (1), 6–16.
Monnier, L., Mas, E., Ginet, C., et al., 2006. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. J. Am. Med. Assoc. 295 (14), 1681–1687.
Moran, C., Phan, T.G., Chen, J., et al., 2013. Brain atrophy in type 2 diabetes: regional distribution and influence on cognition. Diabetes Care 36 (12), 4036–4042.
Nandipati, S., Luo, X., Schimming, C., Grossman, H.T., Sano, M., 2012. Cognition in non-demented diabetic older adults. Curr. Aging Sci. 5 (2), 131–135.
Novak, V., Zhao, P., Manor, B., et al., 2011. Adhesion molecules, altered vasoreactivity, and brain atrophy in type 2 diabetes. Diabetes Care 34 (11), 2438–2441.
Oosterhof, N.N., Wiestler, T., Downing, P.E., Diedrichsen, J., 2011. A comparison of volume-based and surface-based multi-voxel pattern analysis. Neuroimage 56 (2), 593–600.
Pereira, J.B., Ibarretxe-Bilbao, N., Marti, M.-., et al., 2011. Assessment of cortical degeneration in patients with Parkinson's disease by voxel-based morphometry, cortical folding, and cortical thickness. Hum. Brain Mapp. 33 (11), 2521–2534.
Riecker, A., Grodd, W., Klose, U., et al., 2003. Relation between regional functional MRI activation and vascular reactivity to carbon dioxide during normal aging. J. Cereb. Blood Flow Metab. 23 (5), 565–573.
Schmidt, R., Launer, L.J., Nilsson, L.-, et al., 2004. Magnetic resonance imaging of the brain in diabetes: the cardiovascular determinants of dementia (CASCADE) study. Diabetes 53 (3), 687–692.
Ségonne, F., Dale, A.M., Busa, E., et al., 2004. A hybrid approach to the skull stripping problem in MRI. Neuroimage 22 (3), 1060–1075.
Seo, S.W., Lee, J.-, Im, K., et al., 2012. Cardiovascular risk factors cause cortical thinning in cognitively impaired patients: Relationships among cardiovascular risk factors, white matter hyperintensities, and cortical atrophy. Alzheimer Dis. Assoc. Disord. 26 (2), 106–112.
Takeuchi, A., Matsushima, E., Kato, M., et al., 2012. Characteristics of neuropsychological functions in inpatients with poorly-controlled type 2 diabetes mellitus. J. Diabetes Investig. 3 (3), 325–330.
Tancredi, F.B., Hoge, R.D., 2013. Comparison of cerebral vascular reactivity measures obtained using breath-holding and $CO_2$ inhalation. J. Cereb. Blood Flow Metab. 33 (7), 1066–1074.
Tiehuis, A.M., Vincken, K.L., Van Den Berg, E., et al., 2008. Cerebral perfusion in relation to cognitive function and type 2 diabetes. Diabetologia 51 (7), 1321–1326.
Tucholka, A., Fritsch, V., Poline, J.-., Thirion, B., 2012. An empirical comparison of surface-based and volume-based group studies in neuroimaging. Neuroimage 63 (3), 1443–1453.
Turner, R., Holman, R., Stratton, I., et al., 1998. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. Br. Med. J. 317 (7160), 703–713.
Vuorinen, M., Kåreholt, I., Julkunen, V., et al., 2013. Changes in vascular factors 28 years from midlife and late-life cortical thickness. Neurobiol. Aging 34 (1), 100–109.
Wu, F., Guo, Y., Kowal, P., et al., 2013. Prevalence of major chronic conditions among older Chinese adults: the study on global AGEing and adult health (SAGE) wave 1. PLoS ONE 8 (9).