Cortical volume and perfusion are influenced by vascular risk factors in addition to cognitive status: new insight made available from the ADNI study

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Introduction: Brain atrophy related to neurodegeneration and Alzheimer's disease (AD) has been studied extensively; and although vascular risk factors (VRFs) are known to increase the risk of AD onset[1], little is known about the adverse effects of VRFs on brain structure and perfusion that give rise to cognitive decline. The primary objective of this study was to use a multivariate method, partial-least squares (PLS), to investigate whether VRF status can improve our understanding of regional brain changes relative to a model scenario where cognitive diagnosis is used exclusively. To test this theory data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) were used. Secondary analyses included: 1) an attempt to replicate the primary objective using follow-up ADNI MRI data and 2) characterize the relationship between cerebral blood flow (CBF) and cortical volume.

Methods: Analyses were conducted on participants from the ADNI GO and ADNI 2 datasets. Participants were identified if they had at least two MRI sessions that included both high resolution T1-weignted images and arterial spin labeling (ASL) perfusion imaging[2] and were not diagnosed with AD (i.e. Normal controls, NC, and mild cognitive impairment, MCI, groups). Presence or absence of VRFs (diabetes, hypertension, hypercholesterolemia and smoking) was ascertained for all participants based on medications and medical history. T1-weighted images were previously analyzed using freely available software Freesurfer and summary structural metrics are available for download from the ADNI website[2,3]. We selected 14 regions of interest (ROIs) based on their reported involvement in VRFs (caudal middle frontal(1), pars orbitalis(2), superior temporal(3), anterior cingulate cortex(4), precuneus(5), supramarginal(6) and lingual gyri(7)), their association with dementia (entorhinal cortex(8), hippocampus(9), inferior parietal gyrus(10), posterior cingulate cortex(11), medial orbito-frontal(12) and rostral middle frontal(13)) or both (middle temporal gyrus(14))[4,5]. ASL images were preprocessed using the Centre for Imaging of Neurodegenerative Diseases (CIND) pipeline and the average CBF values in Freesurfer ROIs are also available for download[2,6]. Cortical volumes and CBF were averaged across hemispheres for each ROI. Two predictive models were considered in PLS cortical volume analysis: Model-1) using cognitive diagnosis only (NC, early MCI (eMCI) and late MCI (lMCI)), and Model-2) a combination of cognitive diagnosis as in Model-1 and a binary classification of VRF risk (VRF-low: having 0,1 VRFs; VRF-high: having 2,3 VRFs). PLS was used to generate latent variables (LV) that explained the cortical volume variability across ROIs. Statistical significance of the LVs was determined using 1000 permutation tests ($p<0.05$ for significance). Bootstrap resampling (100 bootstraps) was used to identify brain regions that consistently showed a significant LV pattern (bootstrap ratio >2.3 for significance). Secondary analysis: 1) Replication of the structural PLS result was considered based on the follow-up MRI; 2) PLS was also performed using Model-2 with cortical volume as the outcome measure and regional CBF as predictor variables.

Results and Discussion: ***Primary objective:*** One hundred and thirty two participants were included in the primary PLS analysis on baseline cortical volume data (NC VRF-low: 19, NC VRF-high: 21, eMCI VRF-low: 32, eMCI VRF-high: 29, lMCI VRF-low: 13, lMCI VRF-high: 18). Both models produced a single significant LV ($p=0.003$ and $p=0.002$, respectively). Figure 1, Model-1(top) and Model-2 (bottom), shows that the cortical volume differences were driven by eMCI and lMCI subgroups. Furthermore, Model 2 (bottom) indicates that this effect was specific to VRF-high groups. LV patterns from Model-1 and 2 were significant in ROIs: 1, 2, 3, 5, 8, 12 and 13. Additionally the LV pattern from Model-1 was also detected in ROIs 9 and 14, whereas Model 2 pattern was also seen in ROI 6.

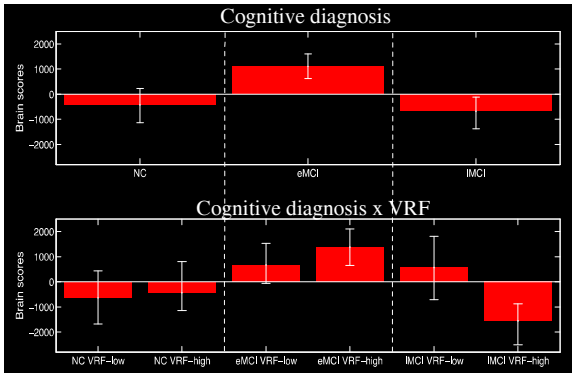

Figure 1: Cortical volume PLS. Top: Model 1- Cognitive diagnosis; Bottom: Model 2 - Cognitive diagnosis + VRF burden

Replication: The follow-up scans were performed 4.7± 4.6 months after the baseline. For the replication test we examined Model-2 only. Again only a single significant LV ($p<0.001$) was observed. EMCI VRF-high and lMCI VRF-high were found to be the highest contributing groups to this LV (eMCI VRF-low was also marginally significant, results not shown). The LV pattern was observed in ROIs: 1, 2, 3, 5, 6, 7, 8, 9, 13 and 14. ***Multi-modality:*** 12 participants were excluded from the CBF vs. cortical volume PLS analysis due to inadequate brain coverage for ASL (sample size: 120, NC VRF-low: 18, NC VRF high: 17, eMCI VRF-low: 29, eMCI VRF-high: 27, lMCI VRF-low: 11, lMCI VRF-high: 18). There was one significant LV ($p=0.002$) that explained the associations between regional CBF and cortical volumes, driven primarily by the eMCI and lMCI groups with low VRF burden (Figure 2), and implicating several ROIs: 2, 3, 5, 6, 10, 11, 12, 13 and 14. In a post-hoc analysis Pearson correlations between CBF and cortical volume were significant in lMCI VRF-low group only in ROIs: 5 ($p=0.03$), 13 ($p=0.05$) and 6 ($p=0.04$) (Figure 3).

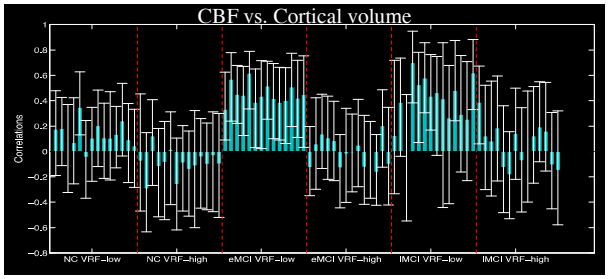

Figure 2: Association between regional CBF and cortical volumes

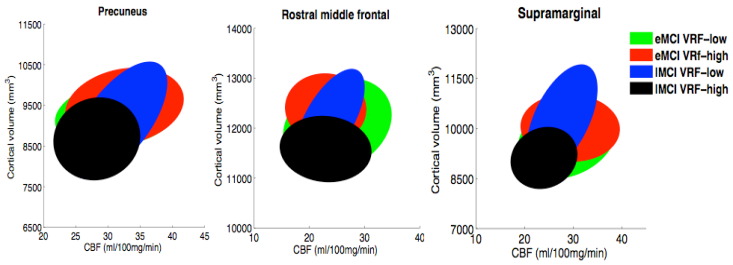

Figure 3: Each error ellipse represents 1 SD around that group's mean

Conclusion: This study demonstrates that variability in cortical volume among MCI adults is significantly influenced by VRF burden. Our primary conclusion is supported by the two secondary analyses. Furthermore, CBF values were predictive of the cortical volume variability but only among the eMCI and lMCI subgroups with low VRF burden (i.e. none or 1 VRF). Three regions (precuneus, rostral middle frontal and supramarginal gyri) showed a particularly strong correlation between the two brain metrics within the lMCI group suggesting their synergistic decline. Results of this study emphasize the importance of considering VRF burden in studies on MCI and dementia.

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References: 1) Luchsinger et. al. Aggregation of vascular risk factors and risk of incident Alzheimer disease. Neurology. 2005; 2) ADNI: http://adni.loni.ucla.edu 3) Hartig M, et al. UCSF Freesurfer methods; 4) Leritz et. al. Thickness of the human cerebral cortex is associated with metrics of cerebrovascular health in a normative sample of community dwelling older adults. Neuroimage. 2011; 5) Fennema-Notestine et.al. Structural MRI biomarkers for preclinical and mild Alzheimer's disease. Human Brain Mapping. 2009; 6) Cuneo D, et al. UCSF ASL Perfusion Processing methods. Dec 4, 2012