Data-driven analysis of Cerebrovascular reactivity reveals regional vascular impairment in individuals with multiple systemic risk factors

Ekaterina Tchistiakova[1,2], David E. Crane[2], Sandra E. Black[2,3], and Bradley J. MacIntosh[1,2]

[1]*Medical Biophysics, University of Toronto, Toronto, ON, Canada,* [2]*Heart and Stroke Foundation Canadian Partnership for Stroke Recovery, Sunnybrook Research Institute, Toronto, ON, Canada,* [3]*Department of Medicine, Division of Neurology, University of Toronto, Toronto, ON, Canada*

Introduction: Cerebral small vessel disease (SVD) is associated with impaired vascular regulation[1] and is considered a major risk factor for stoke[2] and dementia. Cerebrovascular reactivity (CVR), the ability of brain blood vessels to dilate, can serve as an index of cerebrovascular dysfunction. The objective of this study was to determine whether additive vascular conditions, i.e. hypertension (HTN), type 2 diabetes (T2DM) and high cholesterol (Chol.), affect CVR in a group of adults with pre-existing white matter SVD lesions. CVR was measured using two brief CO_2 inhalation challenges during BOLD scanning. CVR regions of interest (ROIs) were defined by functional connectivity resting state networks (RSNs). Specifically, primary sensory (sensorimotor and visual) were chosen because of their high vascular density; the default mode network (DMN) was chosen because it is implicated in neurodegenerative processes.

Methods: Twenty-one participants were scanned with a 3T Philips Achieva MRI system. MRI protocol consisted of a single-shot, gradient echo EPI for BOLD imaging during 1) resting state (RS) and 2) CO_2 inhalation acquisitions. The following parameters were used for BOLD imaging: TR/TE=2000/30ms, flip angle=90°, FOV=230x187mm^2, 40 slices, acquisition matrix=64x64, in-plane resolution=3.59x2.89mm^2, slice thickness=3mm and scan durations of 6m8s and 8m38s for RS and CO_2, respectively. The target end-tidal CO_2 change used in CVR assessment was 10mmHg. High-resolution T1-weighted images were acquired for image registration using: TR/TE=9.5/2.3ms, flip angle=8°,FOV=240x191mm^2, 140 slices, acquisition matrix=256x164, in-plane resolution=0.94x1.17mm^2, slice thickness=1.2mm and scan duration of 8m56s.

Participants were assigned to one of three vascular risk groups based on their pre-existing vascular conditions ("0", "1" and "2 and greater"). BOLD data from RS and CVR conditions were analyzed using temporally-concatenated Independent Component Analysis (FSL MELODIC)[3]. RS-BOLD data were used to generate a set of RSNs, and define ROIs for group comparison based on three networks: sensory-motor, medial visual and default mode network (DMN). These ROIs were used as functional masks in dual-regression [4] to generate subject-specific networks for both the RS and CVR datasets. An average variance-normalized percent BOLD change was calculated for RS and CVR data for each participant for each of the 3 ROIs. Group statistics were run separately on each of the ROIs to examine between-group differences using one-way ANCOVAs for each CVR and RS and controlling for age. A model-based approach using general linear model was used to generate CVR maps (using end-tidal CO_2 trace) to examine the sensitivity of standard CVR analysis and compare its results with ICA-based approach. Group differences in model-based CVR in the three RSNs were tested with an ANCOVA.

Results and Discussion: Age and white matter disease (WMD) burden were similar across the 3 groups (Table I). The 3 RSNs used as functional ROIs are shown in Figure I. There were significant between-group CVR differences in the Sensory-motor network ($F_{2,17}$=3.9, p=0.04) and DMN ($F_{2,17}$=5.5, p=0.014) but not the visual RSN (p=0.955). Figure II shows the BOLD % change and post-hoc analyses indicating CVR is lower in the "Risk>=2" group compared to "Risk=0" in the sensory-motor network. In DMN CVR is lower in the "Risk>=2" group compared to both "Risk=0" and "Risk=1" (p<0.05). By contrast, RS BOLD % was not associated with vascular risk groups (Sensory-motor: p=0.792, Visual: p=0.662, DMN: p=0.991), Figure II. In addition, CVR maps obtained using conventional model-based approach also did not produce a significant association with vascular risk group (Sensory-motor: p=0.123, Visual: p=0.316, DMN: p=0.152), results not shown.

	N	Age (mean±SD)	WMD (median+range)
Group0	6	71.9±8.0	22.1cc (2.4-52.1cc)
Group1	7	72.7±12.0	14.4cc (0.1-70.6cc)
Group2	8	75.0±10.8	19.4cc (0.8-56.6cc)

Table I. Age and white matter disease burden for 3 groups

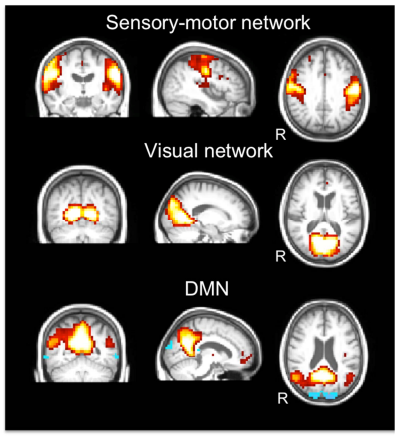

Figure I. RSNs selected for between-group comparisons

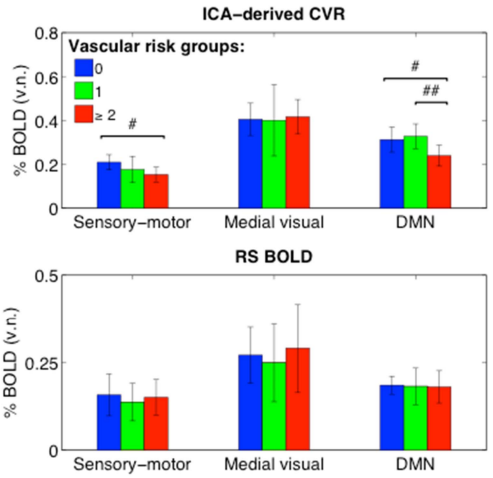

Figure II. Mean and SD for variance-normalized %BOLD change, %BOLD (v.n.), for 3 vascular risk groups in 3 networks during CVR and RS. Also shown between-group comparisons: # p<0.05 and ## p<0.01 (ANCOVA).

Conclusion: Our findings indicate there is an additive effect of systemic vascular conditions on the brain among SVD that are an at-risk population for developing dementia. The number of vascular risk factors was associated with regional CVR decreases, namely in sensory-motor and DMN RSNs. Our results are novel and may be relevant to Alzheimer's disease (AD) research. The DMN has for example been reported as dysfunctional in AD[5]. Others posit that there is a link between vascular conditions and AD risk. Our work demonstrates that the type of fMRI data (i.e. CVR vs. RS) as well the analysis procedures (i.e. ICA vs. model-based) are important considerations in the development of imaging biomarkers of neurodegenerative processes.

References: 1. Makedonov I, et al. Cerebral small vessel disease in aging and Alzheimer's disease: A comparative study using MRI and SPECT. *European Journal of Neurology*. 2013;20(2):243-250.
2. Poels MMF, et al. Assessment of cerebral small vessel disease predicts individual stroke risk. *Journal of Neurology, Neurosurgery and Psychiatry*. 2012
3. Beckmann CF, et al.. Probabilistic independent component analysis for functional magnetic resonance imaging. *IEEE Trans Med Imaging*. 2004
4. Filippini N, et al. Distinct patterns of brain activity in young carriers of the APOE-ε4 allele. *Proc Natl Acad Sci U S A*. 2009
5. Schwindt GC, et al. Modulation of the default-mode network between rest and task in alzheimer's disease. *Cerebral Cortex*. 2013
6. Cechetto DF, et al. Vascular risk factors and alzheimer's disease. *Expert Review of Neurotherapeutics*. 2008;8(5):743-750.