A Pilot Study of Early Cognitive And Brain Imaging Changes Associated With Risk Factors for Cardiovascular Disease

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Background:

Early cognitive impairments associated with CV disease risk factors are subclinical, they are infrequently identified in the patient's medical history or during routine medical care. Such mild cognitive impairments, even if not immediately obvious to the physician, may impact preventive care, medication adherence, clinical follow-up, and quality of life. Cognitive impairment in individuals at risk for vascular pathology, but who have not suffered clinical stroke, suggests the presence of a cognitive prodrome for vascular neurodegenerative disease [1]. This cognitive impairment likely reflects subclinical cerebral disease. Unlike the brain, other end-organs which are damaged by prolonged exposure to vascular risk factors, such as the retina and the heart, are routinely investigated for morphological and functional changes. However, available means to study the brain as an end-organ of pathological processes associated with vascular risk factors in patients with subclinical disease had been limited. We hypothesize that these CV disease risk factors will individually, and to a greater extent in combination, lead to disruption of brain connective networks supported by myelinated white matter fibers, which in turn will lead to deficits in functional signaling between various brain networks important for normal cognitive functions. Furthermore, we hypothesize that disruptions of brain connective networks associated CV disease risk factors is mediated, in large part, by cerebral micro-vascular atherosclerotic changes, which will be unrelated to any macro-vascular atherosclerotic changes. In this pilot study we will use fMRI, resting state fMRI and DTI to study the relationship of the various brain pathologies with cardiovascular risk factors (CVR).

Methods:

Subjects: 10 subjects with an elevated risk for cardiovascular disease (Coronary Artery Calcium (CAC) score > 400) [2] who are “apparently” free of cardiovascular and cerebrovascular disease and 10 age-, gender-, and ethnically matched healthy comparison subjects with a low risk for cardiovascular disease (Coronary Artery Calcium (CAC) score = 0).

Imaging: all scans were performed on a Siemens 3T Skyra with a 20Ch head and neck coil. A comprehensive imaging protocol was applied consisting of the following sequences: Dual Echo TSE (PD-T2), Field Map for B_0 correction of BOLD scans, GE-EPI BOLD N-Back, GE-EPI BOLD Resting State fMRI, DTI Diffusion Tensor Imaging (70 directions and bi-directional phase encoding, 3D-T1-MPRAGE, Ax-T2-FLAIR, ASL - Perfusion pASL, Susceptibility Weighted Imaging (DWI). Total imaging time: 1.5 hrs. For the current abstract only Working memory N-Back fMRI, rsfMRI and DTI were analyzed.

Analysis: DTI were analyzed using FSL (Eddy current correction, FA calculations), scans were normalization to ICBM template, Tract Based Spatial Statistics (TBSS) were computed and GLM to test for group differences was computed. rsfMRI were analyzed using FSL Melodic and 20 networks were selected. GLM test for group differences were computed.

Results: Cognitive performance scores and retain time were significantly inversely correlated with CAC scores. Diffused reduction in FA is associated with high CVR as measured using CAC (Fig 1). Increased CVR is correlated with increased activation in working memory tasks. Increased CVR is correlated with decreased connectivity in multiple networks as detected by resting state fMRI (Fig 2).

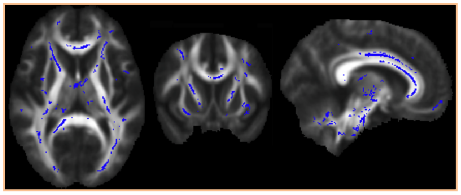

Figure 1: TBSS FA comparisons between high risk and low risk CAC scores. Blue is low risk has higher FA than high risk CAC ($p<0.05$)

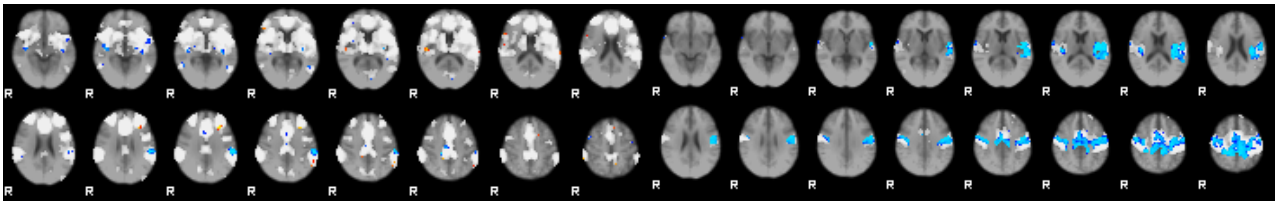

Figure 2: rsfMRI group comparisons (shown are Default mode and auditory network). Blue is high-risk CAC scores lower than low risk CAC scores. Significant voxels shown in color overlaid on resting state network (white) overlaid on grey anatomical MRI

Conclusion:

Reduced structural connectivity leads to poor signaling. Intact networks compensate for reduced connectivity. We have shown that fMRI and DTI can detect changes in functional and structural connectivity in the brain in subjects that are otherwise asymptomatic but have underlying CVR. A larger study will be needed to confirm these results. The results would enhance our ability to identify cognitive and brain changes in asymptomatic persons at risk for CV disease in order to develop interventions to improve compliance with vascular health lifestyle changes and medical treatment.

[1]: van den Berg et al. Biochim Biophys Acta. 2009 May;1792(5):470-81. [2] Detrano, R., et al., N Engl J Med, 2008. **358**(13): p. 1336-45.