Effects of Cardiovascular Disease Risk Factors on Regional Cerebral Blood Flow in Dementia

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Introduction: Perfusion studies of dementia using MRI, SPECT, and PET imaging have generally reported hypoperfusion in the temporoparietal and frontal regions, and the posterior cingulate gyrus. In contrast, we observed both hypo- and hyper- perfusion in mild cognitive impairment (MCI) and early Alzheimer's disease (AD) subjects relative to normal controls. Cardiovascular disease (CVD) risk factors can influence regional cerebral blood flow (rCBF), thus biasing the scientific conclusions. The goal of our study was to determine if regions of hyperperfusion in the MCIs and ADs remained significant after controlling for CVD risk factors.

Methods: Data were acquired under the University of Pittsburgh Cardiovascular Health Study Cognition Study using a 1.5 T GE Signa MRI (LX). Absolute CBF maps of gray matter were created for 104 elderly volunteers (38 healthy controls, 29 MCIs, 37 early ADs) by multi-slice continuous arterial spin labeling (CASL)[1]. The CBF maps were calculated using the kinetic model of CASL[2] and the assumption that gray matter CBF was a global constant. A deformable atrophy-corrected registration method was used to warp the CBF maps to the standard colin27 brain space. The warped CBF maps were smoothed with a 6 mm Gaussian kernel. Image-based voxel-by-voxel t-tests were performed between each group (healthy controls, MCIs and ADs) using Statistical Parametric Mapping (SPM2, Wellcome Department of Cognitive Neurology) and customized to correct for differences in the functional volume scanned in the different subjects. Voxels that were shared by at least half of subjects in each group were counted in the t-test analyses. Cluster-level p-values were calculated to correct for the false positives from the voxel-level multiple comparisons[4].

We selected the statistically-significant clusters of hyperperfusion[4] (cluster-level $P < 0.02$) as our regions of interest (ROIs) for the risk factor regression analysis. Average rCBF for each ROI was obtained from each individual subject. Only those voxels with valid gray matter rCBF values were used in the quantification of rCBF for each ROI. Subjects with less than 100 voxels in the ROI were excluded from further statistical analyses.

We used a multiple-regression model[5] to estimate regression coefficients and performed significance tests to identify the independent contribution of each risk factor (age, gender, education, race, apoe4 allele, heart disease, diabetes, hypertension) to rCBF. Age, hypertension, gender had the most significant effects on rCBF out of the 8 risk factors. We further compared the group differences among the normal controls, MCIs, and early ADs, by controlling for age, hypertension and gender using the one-way analysis-of-covariance (ANCOVA) model. The purpose of the ANCOVA was to exclude group differences that resulted from an imbalance from these 3 risk factors. A multivariate linear regression between the rCBF and 3MSE score, age, hypertension, gender was calculated to investigate the correlation of rCBF with the cognitive status. Both F- and t- tests were performed to assess the specific effect of 3MSE on rCBF after controlling for the effects of other variables.

Results & Discussion: The targeted hyperperfusion ROIs were left hippocampus, left subcallosum, right caudate and right amygdala (MCIs), and right anterior cingulate gyrus (ADs), compared to normal controls. The Z-scores of MCIs and early ADs vs. normal controls for the ROIs were calculated to illustrate the group differences after controlling for the 3 risk factors (age, hypertension, gender) in Fig. 1. rCBF in the right anterior cingulate gyrus had the most significant negative correlation with 3MSE (the regression coefficient of -0.6943, two-tailed p-value = 0.0056).

The rCBF of the targeted ROIs remained significantly higher compared to the normal controls even after controlling for the selected risk factors. rCBF in the right anterior cingulate gyrus was negatively correlated with 3MSE, suggesting the existence of an active compensatory mechanism in CBF during the progression of dementia.

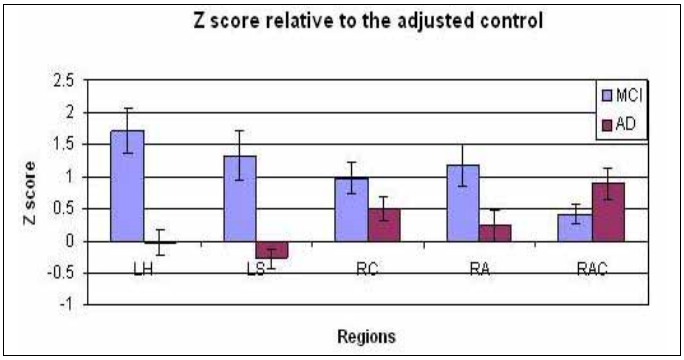

Figure 1: Comparison of CBF of MCIs and ADs relative to normal controls for selected ROIs after controlling for age, hypertension, and gender. LH: left hippocampus, LS: left subcallosum, RC: right caudate, RA: right amygdala, RAC: right anterior cingulate gyrus.

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