Impact of Hypertension and Aging on Resting State BOLD Response to Heart Rate Variation

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Target Audience: neuroimaging clinicians and researchers interested in cerebrovascular physiology; fMRI researchers

Introduction: Non-neuronal physiological fluctuations contribute significantly to blood oxygen level-dependent (BOLD) signal fluctuations in resting state fMRI (rs-fMRI)[1]. Cardiac and respiratory signal components have been represented by the RVHR model[1], where slow-varying responses to perturbations in respiratory volume (RV) and heart rate (HR) are modeled as linear filters. Here, we examine the shape of the cardiac filters, with the aim of extracting information on natural or pathological changes in neurovascular autoregulation.

Method: With IRB approval, we scanned 10 healthy young volunteers (age 30±6), 8 elderly patients (age 79±7) with chronic kidney disease (CKD) and associated hypertension (HTN), and 8 elderly normotensive volunteers with no history of CKD (age 65±5) at 3.0T (GE Healthcare, Waukesha, WI) with physiological monitoring by fingertip photoplethysmography and respiratory belt. We calculated waveforms for RV (standard deviation of respiratory belt recording) and HR (beats/minute) over a 6s sliding window. T1-weighted anatomic images were acquired using 3D IR-FSPGR, registered to MNI space, and segmented into gray matter (GM) and white matter (WM). Whole-brain rs-fMRI data was acquired using 2D GRE EPI (6min duration, flip angle 75°, TE 25ms, TR 2s, voxel 3.4×3.4×3.5mm^3) and preprocessed thusly: RETROICOR[2], registration to MNI space, motion regression, and linear detrending. We fitted each voxel's BOLD time course to the RVHR model: $y(t) = RV(t)*h_r(t) + HR(t)*h_h(t)+\varepsilon(t)$, where respiratory and cardiac filters h_r and h_h were *maximum a posteriori* Bayesian deconvolution solutions[1]. We then examined means of scalar features of h_h, including: 1) maximum [$max(h_h(t))$]; 2) positive area under curve (AUC) [$\int max(h_h(t),0)dt$]; 3) normalized positive AUC [$\int max(h_h(t),0)dt$ / $\int abs(h_h(t))dt$]. Statistical significance of pairwise comparison between groups was determined at α=0.05 using the Wilcoxon rank-sum test with Benjamini-Hochberg procedure for multiple comparisons. Finally, we grouped all voxel-wise h_h within each subject group into 8 clusters using k-means clustering, and compared the set of mean filters from each cluster across subject groups.

Results: Means of all three cardiac filter features were found to significantly differ between the young normals and elderly normals, and between the elderly HTN/CKD patients and elderly normals (Fig. 1). K-means clustering produced three sets of similarly shaped cluster mean filters, with similar cluster sizes (Fig. 2). Consistent with previous research[1], no spatial pattern was observed in the cluster maps.

Discussion: To understand these results, we examine the physiological interpretation of h_h. Following a sudden spike in HR, supply of fully oxygenated blood to the brain increases, reducing deoxyhemoglobin concentration and hence increasing BOLD signal. Thus, any autoregulatory process responding to this perturbation should increase BOLD signal. This corresponds to the positive points in h_h. Maximum h_h measures the amplitude of this response, while positive AUC also accounts for the duration of the response. Normalization by total absolute AUC corrects for inter-subject differences in BOLD signal amplitude. The reduction in response from young to elderly normals may be explained by reduction in oxygenation changes over the cardiac cycle and/or cerebrovascular compliance with aging. However, results for the HTN/CKD group were unexpected. A naïve assumption is that HTN/CKD should further reduce cerebrovascular compliance and autoregulatory response, but we actually observed an increase in response comparing to the elderly normals. This suggests other compensatory mechanisms, which must be ascertained with further investigation and larger numbers of patients.

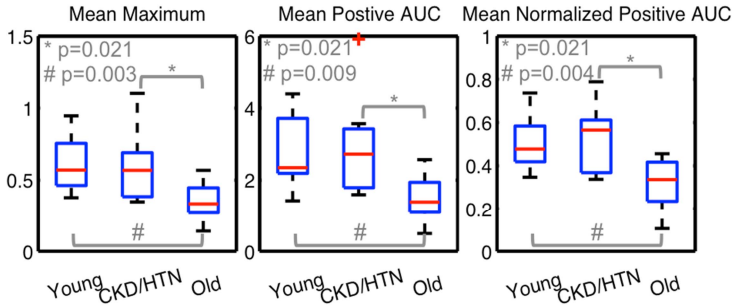

Fig. 1: Group distributions of whole-brain mean cardiac filter features: maximum value, positive AUC), and normalized positive AUC, with p-values for statistically significant pair-wise comparisons. Results for GM and WM are similar and not shown.

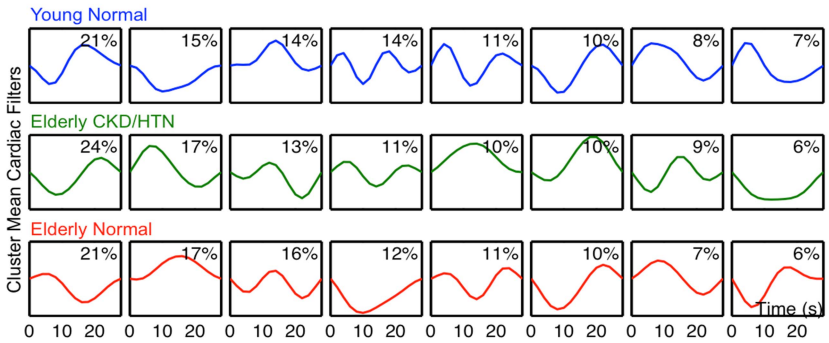

Fig. 2: Mean cardiac filters for k-mean clusters of each group, annotated with the percentage of voxels in each cluster. No spatial pattern is observed in the cluster maps (not shown).

Conclusion: We have identified three features potentially related to the strength of cerebrovascular autoregulatory processes responding to HR variations. Statistically significant differences observed in these features suggest reduction in autoregulation due to aging, and potential obscuring of aging effects by HTN/CKD. This could allow us to further probe the mechanism of autoregulation and the role of HTN/CKD in the process.

References: 1. C Chang *et al.*, NeuroImage, 2009. 2. G Glover *et al.*, MRM, 2000. **Acknowledgements**: Supported in part by NIH 1R01NS066506, NIH 2R01NS047607, NCRR 5P41RR09784, and the Stanford Graduate Interdisciplinary Fellowship program.