Aging-Related Reduction in Physiological Signal Contribution to Resting State fMRI

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Target Audience: fMRI researchers, neuroimaging clinicians and researchers interested in aging

Introduction: Resting state functional MRI (rs-fMRI) records spontaneous blood oxygen level-dependent (BOLD) signal fluctuations in the brain[1]. Conventionally, fluctuations with physiological origins are considered "noise" and removed using techniques including the RVHR method[2], which extracts slow-varying responses to changes in respiratory volume (RV) and heart rate (HR). However, this discarded signal component actually contains valuable information related to perfusion and vascular reactivity, and could reflect natural or pathological changes in neurovascular properties and autoregulatory processes. Thus, in this study, we examine the percentage of rs-fMRI signal variance attributable to RVHR physiological component in young and elderly subjects.

Method: With IRB approval, we scanned 10 healthy young volunteers (age 30±6, 8 male), 8 elderly patients (age 79±7, 6 male) with chronic kidney disease (CKD, defined as baseline eGFR <60mL/min/1.73m^2) and associated hypertension (HTN), and 8 elderly volunteers with normal blood pressure and no history of kidney problems (age 65±5, 1 male) at 3.0T (GE Healthcare, Waukesha, WI) using an 8-channel head coil with physiological monitoring by a fingertip pulse oximeter and a respiratory belt positioned below the diaphragm. Time courses for RV (standard deviation of respiratory waveform) and HR (heart beats per minute) were computed over a 6s sliding window. High-resolution T1-weighted whole-brain anatomic images were acquired using a 3D IR-FSPGR sequence, registered to MNI space, and segmented into gray matter (GM) and white matter (WM). 6min of whole-brain rs-fMRI data was acquired using a 2D GRE EPI sequence (flip angle 75°, TE 25ms, TR 2s, voxel 3.4×3.4×3.5mm^3). Preprocessing consisted of: fast-varying physiological noise removal using RETROICOR[3], realignment and registration to MNI space, motion regression, and linear detrending. The time course was then fitted to the RVHR model: $y = RV*h_r + HR*h_h + \varepsilon$, where filters h_r and h_h were *maximum a posteriori* Bayesian deconvolution solutions[2]. Finally, the percentage variance accounted for by the RVHR model (PV-RVHR) was calculated in GM and WM via linear regression, and compared between populations.

Results and Discussion: Using α=0.05 with Bonferroni correction, mean PV-RVHR in GM, WM and whole-brain was found to differ significantly between young normals and CKD/HTN patients, and between young and old normal (Fig. 1). This indicates that aging is associated with a lower percentage contribution of physiological variations to resting state BOLD fluctuations. There was no statistically significant pair-wise difference in spatial standard deviation (SD) of PV-RVHR between populations (Fig. 1). We examined potential covariates including mean breathing rate, mean/SD of HR, and mean/SD of RV, but found no strong correlation. Previous research[4] has found an increase in resting state BOLD fluctuations with age. Our results then suggest that there may be an increase in non-physiological BOLD fluctuations, a reduction in absolute physiological signal variation, and/or a reduction in BOLD signal's synchrony with RV and HR. Possible causes include lower baseline tissue oxygenation, reduced cardiac and respiratory effectiveness, reduced autoregulation, and change in neurovascular biomechanical properties resulting in a limited ability for blood volume to change in response to physiological stimuli. CKD and HTN do not seem to affect PV-RVHR, as shown by the lack of statistically significant difference between the two elderly populations. Within each population, our PV-RVHR maps (Fig. 2) were similar in appearance and diversity as those presented previously[2]. There was no strong visual correlation with brain structure, and we did not find statistically significant difference between GM and WM.

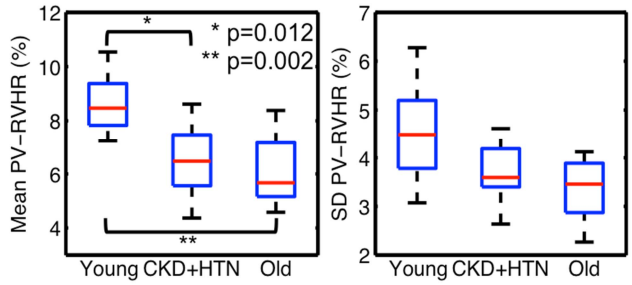

Fig. 1: Distribution of whole-brain (left) spatial mean and (right) SD of the percentage of variance attributable to RVHR (PV-RVHR) across subjects, and p-values for statistically significant pair-wise comparisons. Corresponding plots for GM and WM are similar and hence not shown.

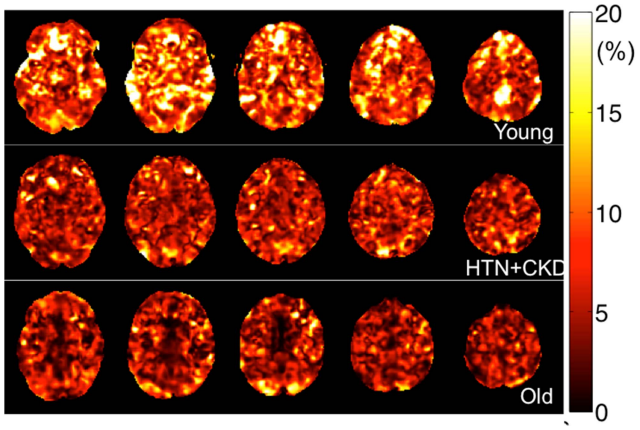

Fig. 2: Representative maps (5 corresponding slices) of PV-RVHR in the three populations. Significant inter-subject spatial variation was observed within each population.

Conclusion: In elderly normal and HTN/CKD populations, we observed a reduction in the percentage of BOLD signal variance attributable to physiological variations by the RVHR model. This suggests an increase in non-physiological variation, or a reduction or change in BOLD response to cardiac and respiratory stimuli, which could be caused by aging-related changes in neurovascular properties or autoregulatory processes. HTN/CKD was not observed to be a significant factor.

References: 1. M Fox & M Raichle, Nat Rev Neurosci, 2007. 2. C Chang *et al.*, NeuroImage, 2009. 3. G Glover *et al.*, MRM, 2000. 4. I Makedonov *et al.*, PLOS ONE, 2013. **Acknowledgements**: Supported in part by NIH 1R01NS066506, NIH 2R01NS047607, NCRR 5P41RR09784, and the Stanford Graduate Interdisciplinary Fellowship program.