AN INVESTIGATION OF THE EFFECT OF AGING ON CARDIAC PULSATILITY IN BOLD FMRI

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INTRODUCTION

Resting state fMRI is a popular technique in the study of neural connectivity. Signal fluctuations due to cardiac and respiratory sources, known as physiological noise, are typically filtered or otherwise removed from fMRI time series[1,2]. Physiological noise may contribute to false positive connectivity[3], and is in general an undesired feature of fMRI data. Cardiac pulsatility is caused by the periodic inflow of blood into brain tissue and intracranial space. The theory of Moody posits that mechanical pulsation in cerebral vessels may provide an index of cerebrovascular health[4]. This mechanical pulsatility is implicated in brain aging and potentially in cerebrovascular pathology like small vessel disease. Small vessel disease is understood to be a main reason for the formation of white matter hyperintensities (WMHs) in older individuals. The purpose of this paper is to characterize physiological cardiac signal in resting state fMRI and to compare data from young controls, elderly controls, and elderly patients with significant volumes of WMHs. The ultimate goal is to extract meaningful data about disease state from information that is currently mainly thought of as being noise.

METHODS

The cardiac BOLD signal was critically sampled by collecting between 2 and 4 slices at 4Hz. Gradient Echo-Echo Planar Imaging (GE-EPI) scans were acquired at a TR of 250ms on a 3T GE scanner. An echo time of 30ms, a flip angle of 34°, and a 3x3x5mm voxel size were used. As opposed to whole brain fMRI, a limited number (2-4) of axial slices was chosen to accentuate inflow effects. The slices were centered at the top of the ventricles. The heart rate was recorded using a pulse oximeter. High resolution T1 weighted images were acquired for tissue class segmentation, and time of flight scans were acquired to visualize intracranial blood vessels. Data were collected for 9 young controls (NCs, 22-27 years of age), 5 older controls (EPs, 62-67 years of age), and 2 patients with significant WMH burden (SVDs)

Images were motion corrected, and the tissue class masks were eroded with a 3mm Gaussian kernel to reduce partial voluming effects and exclude large blood vessels. Each voxel's time course was transformed to the frequency domain. Cardiac power maps were created by integrating the power within 0.02Hz of the heart rate at each voxel. For each scan, 3-voxel clusters with the greatest mean cardiac power were found and ranked in order of decreasing power. A correlation analysis was then performed between the mean time courses of the high power seed clusters and the rest of the brain. The percentage of voxels in the cerebrospinal fluid, gray matter, and white matter (CSF, GM, WM) classes that was correlated to the high cardiac power clusters was found. Multiple comparisons were corrected for ($p=0.05$ at cluster level) and an F-value of 4 was used as the cutoff (FSL FEAT)[5]. The percentage correlation results from the top seven clusters were averaged for each scan. As a complementary analysis, the mean relative change at the cardiac frequency was determined for each tissue class in each scan. Relative change at a voxel is equal to the mean amplitude at the cardiac frequency divided by the mean intensity. Mean amplitude was calculated by dividing the integrated area within 0.02Hz of the heart rate by 0.04Hz.

RESULTS

Three main results were found.

1) The percentage of GM and WM voxels that were correlated to seeds with high cardiac power differed between the young and elderly

controls (51% and 72% of GM in NCs and ECs respectively, p=0.03; 39% and 55% of WM in NCs and ECs respectively, p=0.02).

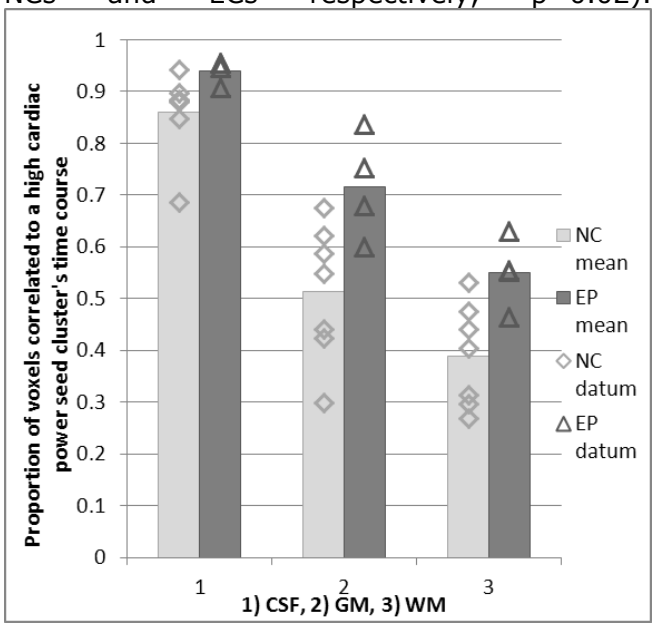

Figure 1 Proportion of voxels in different tissue classes whose time courses are correlated to seed clusters with high cardiac power (p=0.03 for the comparison between NC and EP GM; p=0.02 for the comparison between NC and EP WM; NC: young controls, EP: elderly controls).

2) The relative change of the BOLD signal at the cardiac frequency in GM and WM voxels differed between the young and elderly controls (0.13% and 0.22% in GM, p=0.01; 0.08% and 0.10% in WM, p<0.01). See Figure 2.

3) There were no differences between the elderly controls and SVD patients with respect to the cardiac signal in GM. But, there was a pronounced difference (greater than twofold) in the relative change metric in WM. See Figure 3.

DISCUSSION

The effects of cardiac pulsatility were found to be significantly different between young and older healthy individuals, in grey and white matter regions of the brain (Figure 1, 2). The difference in cardiac pulsatility between the NC and EP cohorts may be driven by vessel hardening. This is akin to the theory proposed by Moody, which states that hardened venules restrict outflow of blood and reflect more of the cardiac waveform into the upstream circulation. As a result, cardiac features are seen in a greater percentage of the brain voxels and their relative magnitude is also greater.

The results comparing ECs to SVDs are preliminary because the sample size for SVDs is currently 2. That said, the data show that there is a difference between the normal appearing WM in the EP and SVD cohorts. It is not solely the lesions that have altered hemodynamics: the healthy appearing WM in these patients has a twofold greater relative BOLD change at the cardiac frequency than WM in the controls. It is possible that this reflects a global cerebrovascular condition that is present in the SVD patients but not in the controls. The white matter lesions may be the only signs of this change that are visible on structural FLAIR scans. The WM that appears normal on FLAIR in

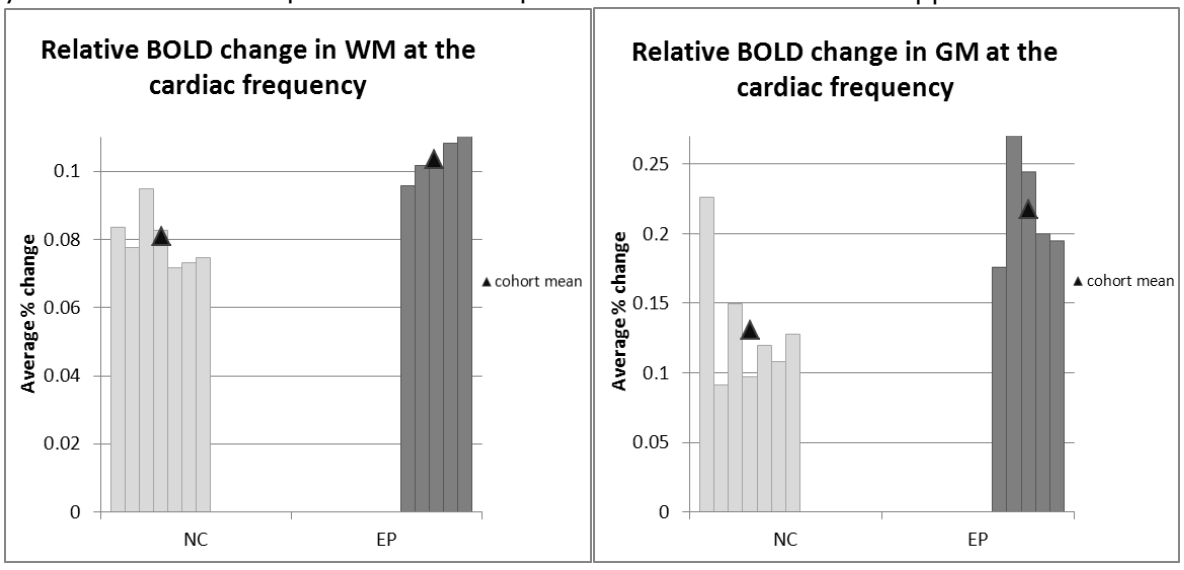

Figure 2 Relative BOLD change at the cardiac frequency in different tissue classes in different subjects (NC: young controls, EP: elderly controls).

SVD patients may not have progressed to demyelination and gliosis yet, but it already has an altered hemodynamic state.

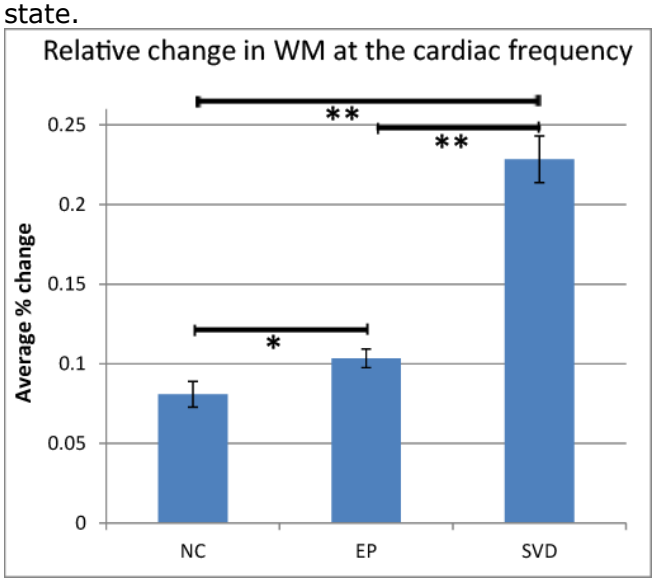

Figure 3 Average relative BOLD change at the cardiac frequency in normal appearing WM for the young controls (NC), elderly controls (EP), and small vessel disease (SVD) cohorts (± 1 SD; *: significant difference, $p<0.05$; **: significant difference, $p<0.0001$).

It is also noteworthy that no differences were observed between the EP and SVD cohorts with respect to GM cardiac pulsatility. A global cerebrovascular pathology can be expected to alter the hemodynamics of blood vessels in both GM and WM. However, GM did not show any differences. It is possible that the cerebrovascular pathology that leads to SVD is at such a stage in these patients that the vascular damage that has occurred in the vessels that feed GM has not yet resulted in significant functional changes. WM is generally much less perfused than GM, and a lot of the periventricular WM receives blood largely from the ventriculofugal vessels, which have few anastomoses and are vulnerable to systemic hypoperfusion.

This is consistent with the findings that the presence of WMHs is a predictor of future stroke, Alzheimer's disease, and death[6]. The SVD cohort does not yet differ from the EP cohort in terms of GM cardiac pulsatility, but the WM already shows significant cerebrovascular changes.

Alternatively, the lack of difference between cardiac pulsatility in EP and SVD cohorts can be caused by the presence of adjacent large blood vessels in GM. Variation in the signal from large arteries can potentially mask any small scale pulsatility changes that are caused by small vessel pathology.

CONCLUSION

This study developed a BOLD scanning protocol that allowed the study of cerebrovascular cardiac pulsatility. Data were then used to find differences between the GM and WM cardiac BOLD fMRI signal in normal controls and elderly controls. The methodology was then applied to SVD patients, and showed that there is a difference between the cardiac BOLD signal in the tissue that appears to be normal WM on FLAIR scans in EP and SVD patients.

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