An Index of Low Frequency (0.1 Hz) Spectral Power Predicts Changes in the Amplitude and Shape of the BOLD Response

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Introduction There is growing evidence that the amplitude and shape of the BOLD signal used in most fMRI experiments can be significantly altered by changes in the baseline vascular state [1-4]. Variations in the baseline vascular state due to factors such as medication, age, and disease can lead to differences in the BOLD signal across subjects and experimental conditions that may be misinterpreted as differences in neural activity. Recent theoretical modeling work indicates that the dependence of the BOLD signal on the baseline vascular state may reflect shifts in the biomechanical responsiveness of the neurovascular system [5]. This suggests that a non-invasive measure of these shifts in biomechanical responsiveness could be used to predict changes in the amplitude and shape of the BOLD signal. In this work, we consider a measure based on the normalized power in low frequency (0.1 Hz) components of the BOLD response to a random stimulus pattern. We refer to this measure as the ***0.1 Hz spectral index*.** Since the neurovascular system exhibits a characteristic resonance at around 0.1 Hz [6], our working hypothesis is that as the biomechanical responsiveness of the system changes, its ability to resonate in response to a stimulus will also change. For example, we expect that a decrease in responsiveness will attenuate the resonance power and thus decrease the 0.1 Hz spectral index. In this study, we evaluated the efficacy of the 0.1 Hz spectral index using experiments in which the effects of vasoactive agents and the aging process on the baseline vascular state and the BOLD signal were characterized.

Methods Four healthy subjects (young: ages 25 and 39; old: ages 68 and 69) participated after giving informed consent. Each young subject participated in two separate experiments. One experiment measured the BOLD responses prior to and immediately after the administration of a 200 mg oral dose of caffeine, while the second experiment measured responses under normocapnic and hypercapnic (5% CO_2) conditions. Each older subject participated in one scanning session (normocapnia). A radial flashing (8Hz) checkerboard was used as the visual stimulus. A periodic single trial design (5 cycles of 4 seconds on/40 seconds off) was used to characterize the BOLD hemodynamic response function (HRF), while a randomized design (4 minutes long) was used to compute the 0.1 Hz spectral index, with two repeats of each design. In addition, a 3 minute long resting-state scan was acquired to characterize resting-state fluctuations. Imaging was performed on a GE 3 Tesla Excite system. Three 8mm thick oblique slices (FOV 24cm, 64x64 matrix) through the calcarine sulcus were acquired. For the periodic and randomized designs, BOLD data were acquired with the following parameters (TE = 25 ms, TR = 0.5s, flip angle 45 degrees); for the resting-state scan, the parameters were (TE = 25ms, TR =0.25s, flip angle 40 degrees). In addition, arterial spin labeling (ASL: PICORE QUIPSSII, TI1/TI2 600/1500, TR 2s) was used to quantify cerebral blood flow (CBF) in the resting-state and during a functional block design run (4 cycles 20s/40s on/off). For each subject and condition, BOLD HRF estimates were obtained by averaging over cycles and repeats of the periodic single trial design and over a region of interest (ROI) defined from the functional ASL runs, where the ROI was the same across conditions within each scan session (e.g. across normocapnic and hypercapnic conditions). This ROI was also used to calculate average BOLD responses from the randomized designs and the resting-state scans. After detrending, a power spectra was computed from the average randomized responses, and the 0.1 Hz spectral index was calculated as the power in a frequency band 0.095 to 0.125 Hz normalized by the total power of the response. A resting-state index was computed in a similar fashion.

Results Figure 1 shows the BOLD HRFs and normalized power spectra from one of the young subjects. The normocapnic and uncaffeinated HRFs and power spectra from the caffeine (solid blue) and hypercapnia (dash blue) sessions show good agreement across the two scan sessions, which were separated by 27 days. Consistent with prior findings [2-4], caffeine (red curve) increases the amplitude and speeds up the HRF as compared to the normocapnic and uncaffeinated responses, while hypercapnia (green curve) decreases the amplitude and slows down the HRF. The HRF changes are reflected by changes in the normalized power spectra, with the 0.1 Hz spectral index increasing by roughly 100% with caffeine (red) and decreasing by 33 to 50% with hypercapnia (green). As compared to the HRFs from the young subjects, the HRFs of the older subjects (not shown) exhibited an amplitude decrease and broadening that was accompanied by a decrease in the 0.1 Hz spectral index. Figure 2 plots the (a) peak amplitude, (b) time to peak, (c) full-width half maximum (FWHM), and (d) energy of the HRFs versus the 0.1 Hz spectral index for each of 10 experimental data points. There are 4 data points (corresponding to the 4 HRFs shown in Figure 1) for each of the 2 young subjects and 1 data point for each of the 2 older subjects. Overall, the 0.1 Hz spectral index accounts for 40 to 80 percent of the variance in the HRF parameters across the sample population. In contrast, the resting-state index was found to only account for 5 to 40% of the variance across the sample.

Discussion The 0.1 Hz spectral index accounted for a significant fraction of the variability in the BOLD response across the preliminary sample examined. For example, a decrease in the 0.1 Hz spectral index was significantly correlated with a decrease in the BOLD HRF amplitude and a slowing down of the BOLD response (increased time to peak and FWHM). Recent theoretical modeling work indicates that a decrease in amplitude and a broadening of the BOLD response (e.g. due to hypercapnia or age) reflects a decrease in the responsiveness of the neurovascular system [5]. Thus, the 0.1 Hz spectral index may be considered a non-invasive probe of vascular responsiveness. Because it can be obtained with standard fMRI methods, the 0.1 Hz spectral index is easily integrated into fMRI studies and should prove to be useful as a covariate that will enable investigators to better assess whether BOLD signal differences are due primarily to neural or vascular factors.

References [1] D'Esposito , Nat. Rev. Neuro. 4:863 2003. [2] Cohen , JCBFM, 22:1042, 2002. [3] Kenma and Posse, NIMG 14:642, 2001. [4] Liu NIMG 23:1402, 2004. [5] Behzadi NIMG 25:1100, 2005. [6] Nilsson and Aalkjaer, Mol. Interv. 3:79 2003.

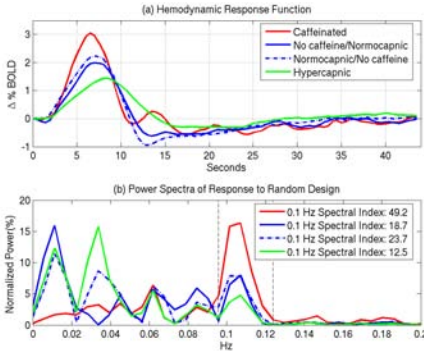

Figure 1

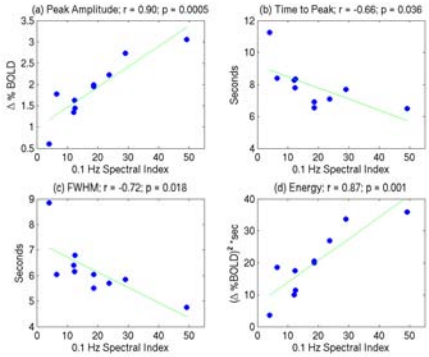

Figure 2