Determining the latency between spontaneous respiration fluctuations and BOLD signal changes

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Introduction:

The blood oxygenation level dependent (BOLD) functional MRI (fMRI) signal has been shown to be correlated with spontaneous fluctuations in end-tidal CO2 during rest. These fluctuations are believed to result from subtle changes in respiration rate and depth [1]. Even though these breathing changes can be externally measured, knowing the latency between respiratory changes and the BOLD signal is required to adequately map and possibly remove the resultant BOLD signal changes. Towards this goal, we measure the magnitude and latency of BOLD signal changes due to spontaneous changes in breathing rate and depth. Furthermore, we compare these measurements derived from resting state data with those obtained from a hypercapnic stress.

Methods and Analysis:

Whole brain sagittal echo-planar images were acquired in 7 healthy volunteers (TR/TE=2000ms/30ms, FOV=24cm, slice thickness=5mm, 27 slices, 165 time points) in order to determine to scope of the fluctuations due to respirations. In one run, subjects were asked to rest for 330s. In another run, subjects were cued to alternate between holding their breath at the end of respiration for 20s and breathing naturally for 40s. Heart rate was monitored using a pulse-oximeter on the index finger and respiration was externally measured by a pneumatic belt on the abdomen at the level of the diaphragm.

Respiration volume per time (RVT), an estimate of end-tidal CO2 [2], was calculated for the resting run by dividing the difference between the maximum and minimum belt positions by the time to the preceding breath. An inverted boxcar function was used to model respiration changes during the breath-holding task. These RVT traces were time-shifted in 1s increments from -10s to +40s and correlated with the raw breath-holding and resting timeseries. The latency and magnitude of the response was determined from the shift with the most negative correlation. This reflects an increase in BOLD signal in response to more shallow breathing or breath-holding.

The latency and amplitude of the signal change for a breath-holding challenge were correlated with the latency and signal change for the resting condition. This analysis was performed both across different voxels in the brain, to assess spatial correlation of resting and breath-holding changes, and across subjects (averaged over regions significantly correlated with resting changes in respiration and breath-holding).

Results:

Changes in the respiration volume per time and BOLD timeseries are highly correlated in regions near blood vessels in both the resting state and breath-holding task (Figure 1). Within subject voxel-wise variability is shown in Figure 2a-b for a representative dataset. A significant correlation is found between the latency of the breath-holding response and the latency of resting state changes in respiration (CC=0.618), and between the amplitude of the signal change in the two tasks (CC=0.866). Across subjects, a correlation of -0.446 is found between the individual average latency for a breath-holding response to the corresponding average resting state latency (Figure 2c-d). On average, signal changes to a 20 s breath-hold are delayed by ~17 seconds. Signal changes to variations in respirations at rest were delayed by ~9 seconds relative to the measured respiration changes. A correlation of 0.726 is found across subjects for the percent signal change for the breath-holding challenge vs. percent signal change due to the resting condition. On average, the breath-holding challenge resulted in a 2 percent signal change while the fluctuations due to spontaneous breathing at rest resulted in a 5 percent signal change.

Discussion and Conclusions:

Significant fluctuations in the fMRI signal were found to correlate with changes in the respiration volume per time. These changes were slower than blood oxygenation level dependent (BOLD) signal changes in response to neuronal activation, occurring approximately 9 seconds after the respiratory changes. These slow respiration changes cannot therefore be modeled with the same response functions used for BOLD fMRI. Strong within subject correlations between the latencies of signal changes to a breath-holding challenge and those during rest and between the amplitude of these signal changes in response to breath-holding vs. rest support the hypothesis that resting-state changes in breathing are at least partially mediated by varying levels of arterial CO2.

References:

1. R.G. Wise et al., *NeuroImage* 21, 2004.
2. J.G. Van den Aardweg, J.M. Karemaker, *Am J Respir Crit Care Med*, 165, 2002.

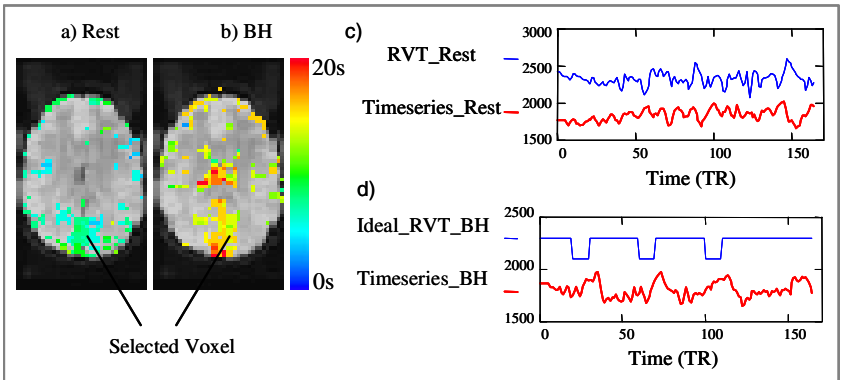

Figure 1: Latency between RVT and BOLD in a) resting run b) breath-holding challenge. Timeseries and RVT trace for c) resting run d) breath holding run

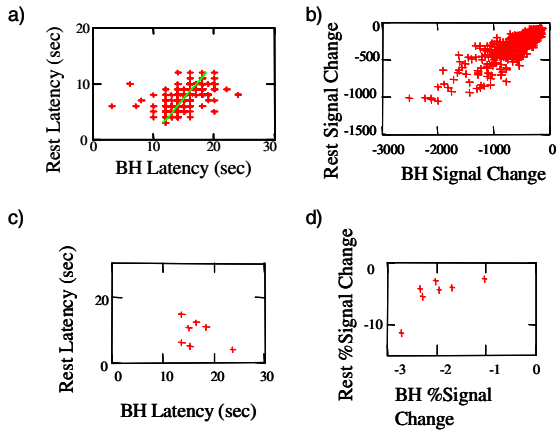

Figure 2: a) Latency and b) Amplitude of breath hold vs. rest across significant voxels in an individual subject c) Average latency and d) Average percent signal change of breath hold vs. rest across subjects. Negative values in b) and d) reflect increases in BOLD signal.