The Respiration Response Function: modeling the temporal dynamics of respiration-volume induced changes in the brain

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Introduction:

Changes in the depth and rate of breathing can cause significant blood oxygenation level dependent (BOLD) signal fluctuations throughout gray matter, mediated by varying levels of arterial CO2 [1,2]. While these variations in breathing can be cued, such as in a breath-holding challenge [3], it is also common for them to occur during rest [1,2]. Accurately modeling the respiration induced signal changes is important for several reasons including: a. reducing respiration related confounds, thereby decreasing false positive detection as well as increasing the location certainty in brain activation mapping, b. increasing temporal signal to noise ratio, thereby improving neuronal activation detection sensitivity, and c. for mapping the vascular information as an end in itself.

Fully removing the variance induced by respiration changes requires a function that is not only correlated with the response, but one that matches the precise temporal shape of the induced signal change. Removing all of the respiration induced fluctuations is particularly important in functional connectivity analysis, a technique that infers functional connections between two or more regions based on the temporal correlation of signal fluctuations [2,4]. Furthermore, respiratory modulations such as breath-holding have been suggested as a way to calibrate the regional variability of the BOLD fMRI signal [5]. However, the response function that best models breath-holding induced signal changes, as well as those resulting from a wider range of breathing variations, including those occurring during rest, has not yet been determined.

The goal of this study is to determine the transfer function between respiration changes, measured by a pneumatic belt placed around the subject's chest, and the induced fMRI signal changes. This transfer function was estimated by analyzing the response to a series of single deep breaths performed once every 60 s amidst otherwise constant respirations. This respiration response function was then used to predict signal changes from a variety of breathing manipulations – breath-holding, cued depth changes, cued rate changes, and natural variations in depth and rate during rest.

Methods:

A series of axial T2*-weighted echo-planar images were acquired from 11 subjects on a 3T General Electric Excite3 MR scanner, with a receive-only eight element RF coil (GE Medical). (TR: 500ms, TE: 30ms, FOV: 24cm, matrix: 64x64, 5mm slice thickness, 600 volumes per run.) In 2 runs, subjects rested with their eyes closed. In other runs, subjects were cued to 1) take one deep breath every 60 seconds, with otherwise constant breathing; 2) change their breathing depth or rate for periods of 15-20 seconds, 3) hold their breath after expiration for periods of 20s. Image volumes were registered in time to correct for subject motion. Heart rate and respiration were recorded with a pulse oximeter and a pneumatic belt, respectively. Respiration volume per time (RVT) changes were estimated by dividing the difference between the maximum and minimum belt positions (the respiration volume) by the time between breaths (the respiration period) [2].

The difference of two Gamma-Variate functions was non-linearly fit to the average response to the single deep breath. This response function was then convolved with the RVT changes, and then correlated with the signal time courses from the other respiration modulations. For comparison, RVT changes were also convolved with the canonical hemodynamic response, and then fit to the data.

Results+Discussion:

A single deep breath resulted in a bimodal response with an early signal increase, peaking at 3 s, followed by a pronounced undershoot of even greater magnitude, peaking at 15 s. This later undershoot is consistent with a decrease in CO2 following a deep breath. The response was fit well by a difference of two gamma variates with the equation,

$$RRF(t) = 0.6\, t^{2.1}\, e^{-t/1.6} - 0.0023\, t^{3.54}\, e^{-t/4.25} \qquad (1)$$

In all subjects, the RVT changes during breath-holding, depth changes, and rate changes, convolved with this response function accurately modeled the respiration induced signal changes (mean t-statistics = 7.1 (Breath-holding), 4.1 (Depth change), 3.0 (Rate change)) (see Fig 1). These respiration-induced changes were generally slower than neuronally-induced BOLD signal changes, and were therefore not as accurately modeled with the canonical Gamma-Variate hemodynamic response function (mean t-statistics = 0.4 (Breath-holding), -0.1 (Depth change), -0.8 (Rate change)). Signal changes induced by variations in breathing during rest appeared to be slightly faster, and were not modeled as well using either the new response function or the canonical hemodynamic response. This may be the result of different physiological processes governing cued versus natural breathing changes.

Conclusions:

Using the average response to a single deep breath, we have determined a new impulse response function that can be used to model respiration induced signal changes across a range of cued breathing manipulations. When used in combination with a pneumatic belt-based measure of respiration, this can be used for a more accurate determination of respiration induced signal change amplitudes, and a more complete removal of confounding respiration induced signal changes.

References:

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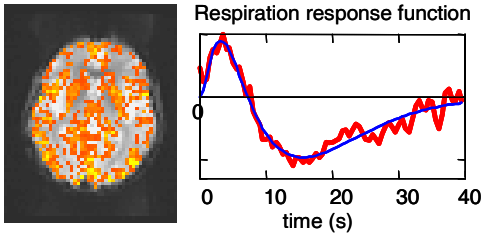

Top) Average response to a single deep breath, used to determine the respiration response function. **Right**) (**Red**): Signal changes in response to breath-holding, Depth changes, Rate changes. Fit of respiration volume per time (RVT) changes convolved with respiration response function derived in this study (**Blue**) or the Gamma- Variate impulse response typically used to model activation (**Green**)