Calibration of BOLD fMRI signal changes using cued and spontaneous breathing variations

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Introduction:

The amplitude of the BOLD fMRI response depends strongly on the properties of the underlying vasculature – the vascular density, sizes of vessels, and proportions of capillaries, venules, and veins within each voxel – with the largest BOLD responses generally occurring in voxels that have the largest fraction of venous blood, typically those containing large draining veins. This dependence has made it difficult to accurately determine subtle differences in the amount of neuronal activity between brain regions or between subjects. To address this problem, earlier studies have suggested calibrating the BOLD signal by using a hypercapnic challenge, which can provide a map of the relative changes in signal from a global increase in blood flow. This was first demonstrated by having subjects breathe elevated levels of CO2 [1,2], but due to the demands of CO2 administration, more recent studies have employed a breath-holding task to modulate arterial CO2 [3]. This respiratory challenge, however, may not be appropriate for all subject groups. Recent studies have shown that natural and spontaneous variations in breathing depth and rate during rest can lead to changes in arterial levels of CO2, resulting in significant BOLD signal changes [4,5]. This suggests that monitoring the fluctuations of a subject's breathing during rest, or having the subject perform breathing manipulations other than breath-holding, can be used to calibrate neuronally-induced BOLD signal changes.

In this study, we compare spatial variations in the amplitude of task-related BOLD signal changes during a visual stimulus to respiration-induced signal changes resulting from 1) breath-holding, 2) cued depth changes, 3) cued rate changes, and 4) normal fluctuations in depth and rate during rest. These respiration changes are then used to calibrate the BOLD response amplitude.

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 (General Electric, Waukesha, WI). (TR: 500ms, TE: 30ms, FOV: 24cm, matrix: 64x64, 5mm slice thickness, 600 volumes per run.) In 2 runs, subjects rested with their eyes closed, and in a 3rd run, subjects viewed a contrast-reversing checkerboard alternated with a gray fixation screen in a blocked design. In 4 additional runs, subjects were cued to 1) take one deep breath every 60 seconds, with otherwise constant breathing; 2 & 3) change their breathing depth or rate for periods of 15-20 seconds, or 4) 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. RETROICOR was used to reduce signal fluctuations at the cardiac and primary respiration frequencies [6]. 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) [5].

A response function to model respiration induced changes was determined from the average response to the single deep breath. This was convolved with the RVT changes, and fit to the signal changes in the other tasks. BOLD response amplitudes and latencies were determined by calculating the correlation of the response with task timing convolved with a gamma-variate function. For both task- and respiration-related analyses, the regression was repeated with different temporal shifts of the ideal response, and the latency that gave the best fit was used in each voxel. Task-induced and respiration-induced signal changes were compared within the active voxels of the visual cortex. A calibrated BOLD response was produced by dividing the BOLD response amplitude by the normalized respiration response amplitude.

Results:

The amplitude of the task-induced BOLD response across the activated region of the visual cortex was significantly correlated with the respiration-induced signal changes during breath-holding, as well as cued depth changes, rate changes, and natural changes in respiration depth and rate during rest (see Fig. 1). (Mean spatial correlation coefficient (averaged across subjects) of 0.51 for Depth, 0.58 for Rate changes, 0.62 for Breath-holding changes, and 0.55 for resting variations). The respiration-induced signal fluctuations during rest were of the same magnitude, and in some cases even larger, that the breath-holding induced changes. Calibration of the task-induced BOLD fMRI response shifted the peak of the visual activation from voxels near the sagittal sinus to more lateral and medial cortical regions. Calibrated maps of activation were consistent for all breathing manipulations and variations (breath-hold, depth change, rate change and rest). Fig.1 shows the results for calibration using resting variations in breathing.

Conclusions:

The significant correlation between task-induced BOLD signal changes and respiration induced changes during rest and cued changes in depth and rate strongly suggest that performing breathing manipulations other than breath-holding, or simply monitoring the subject's breathing during rest, can be used as a way to calibrate the BOLD response amplitude, allowing one to remove large fluctuations in BOLD response amplitude across space, and across subjects that are due purely to variations in blood volume, blood vessel size, or the types of vessels. This can be performed more easily in fMRI than an administration of CO2 or breath-holding, and can enable the application of calibration across a wider range of subjects and patient groups.

References:

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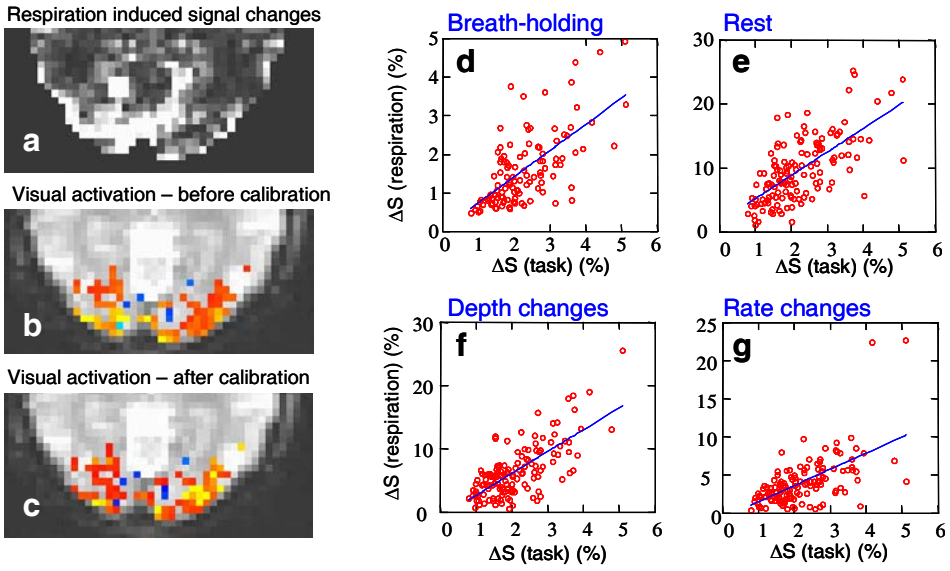

Figure 1: a) Respiration induced signal changes during rest **b)** Visual activation (before calibration) **c)** Visual activation after calibration using respiration fluctuations during rest. **d-g)** Correlation between task-induced and respiration-induced signal changes for active voxels in the visual cortex.