Comparison and Validation of fMRI Calibration Techniques

R. M. Birn[1], D. Handwerker[1], and P. A. Bandettini[1]

[1]Laboratory of Brain and Cognition, National Institute of Mental Health, Bethesda, MD, United States

Introduction:

The amplitude of the blood oxygenation level dependent (BOLD) fMRI signal depends strongly on the properties of the underlying vasculature, particularly the baseline blood volume, with the largest signal changes generally occurring in large vessels. A larger BOLD response in one part of the brain, or in one subject, therefore does not necessarily reflect greater neuronal activity. To address this problem, studies have suggested calibrating the BOLD signal by using a hypercapnic challenge, such as an administration of CO2 or breath-holding, which can provide a map of the relative changes in signal from a global increase in blood flow (1-3). Similar measures for calibration can be derived from other cued breathing variations, or even from variations in the fMRI signal at rest (4-6). While these techniques generally decrease the amplitude of responses in large vessels and shift the hotspot of activation, whether or not these methods can reveal more subtle spatial differences in the amount of neuronal activity has not yet been carefully studied. In this study we test various calibration techniques, and compare their ability to pull out subtle variations in neuronal activity.

Methods:

Eleven subjects were presented with a blocked design (20s stimulation/40s fixation) visual contrast-reversing checkerboard stimulus, where one visual hemi-field (left or right) was at a lower contrast than the other (5% vs. 100% contrast). The BOLD response should be greater in the hemi-field with the higher contrast stimulus. The side that had the higher contrast was alternated for each block. This allowed us to also compute the within-voxel response to varying stimulus contrast. During this stimulus, a series of T2*-weighted echo planar images were acquired on a 3T GE Excite MRI scanner. (TR:2s, TE:30ms, resolution: 3.75x3.75x5mm^3, 27 sagittal slices, 165 images per run.) In 4 additional runs, subjects were cued to 1) hold their breath for 20s periods, 2 & 3) change their breathing depth or rate for periods of 15-20 seconds, or 4) rest with eyes closed. Heart rate and respiration were recorded with a pulse oximeter and a pneumatic belt, respectively.

A measure of the spatial heterogeneity of the BOLD response used for calibration was derived in 6 ways: either by fitting the time course of respiration volume per time (RVT)(7) changes to signal response to 1) breath-holding, 2) cued depth changes, 3) cued rate changes, or 4) rest; and by computing the temporal standard deviation of the resting time course either 5) before or 6) after removing physiological noise. A calibrated BOLD response was produced by dividing the BOLD response amplitude by one of these 6 measures. As an alternative, we also investigated regressing out (rather than dividing by) these measures.

Results:

While the BOLD response should be greater in the hemisphere seeing the higher contrast stimulus, considerable overlap in response amplitudes across hemispheres was observed (Fig 1b). Consistent with earlier studies, the BOLD response amplitude was significantly correlated with respiration-induced changes during rest (Fig 1a), breath-holding, cued depth changes, and cued rate changes. In addition, there was a strong correlation of the BOLD response amplitude with the standard deviation of the resting time course, both before and after removing cardiac and respiratory fluctuations. Spatially regressing out these measures from the BOLD response to the visual stimulus reduced the standard deviation of visual response amplitudes within each hemisphere (Fig 1d), and slightly improved the ability to differentiate visual response amplitudes between the two hemispheres. However, considerable variability in the response amplitude within each hemisphere remained even after calibration. The best calibration was obtained by using either the amplitude of the RVT fit in the resting run, or the standard deviation of the resting run, both before and after removing physiological noise (Fig 1e). Calibrating the response by dividing by the respiration-induced response amplitude or temporal standard deviation increased the variance in some subjects, resulting in a worse differentiation of the response to the high and low contrast stimulus.

Conclusions:

The various measures of the spatial heterogeneity of the fMRI response that have been used for BOLD calibration – breath-holding, cued breathing manipulations, respiration induced signal changes at rest, and the standard deviation of the time course at rest – account for some of the spatial variability in the amplitude of the BOLD response, and removing this variation slightly improves the ability to see subtle variations in neuronal activity. However, significant variability in the amplitude of the BOLD response across the brain remains, which is not explained by these vascular measures.

References:

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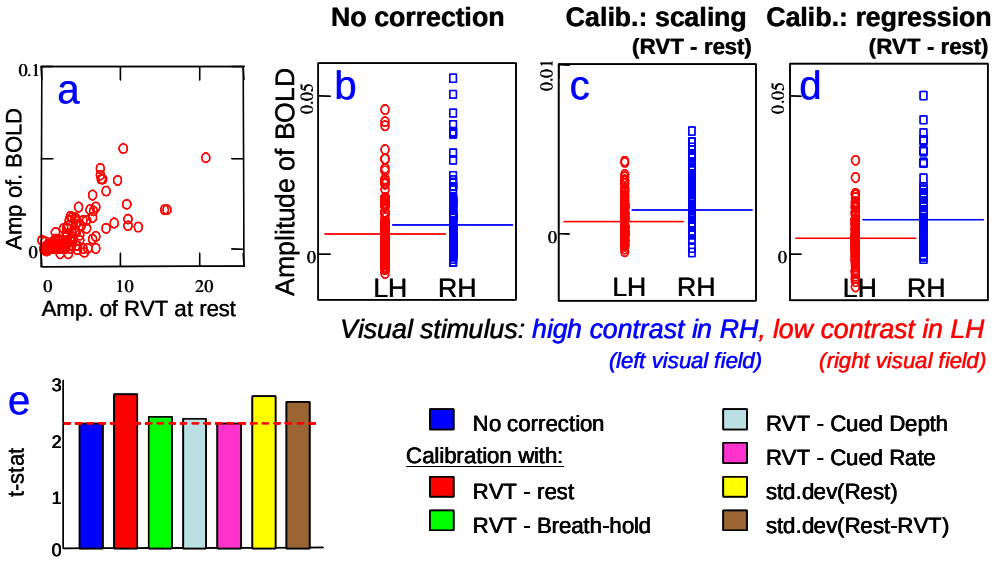

a) Amplitude of BOLD response vs. amplitude of respiration-induced signal change at rest. **b**) Amplitude of BOLD responses in Left (**LH**) and Right (**RH**) Hemisphere before (**b**) and after (**c,d**) calibration using the amplitude of the resiration induced signal changes at rest (i.e. the signal changes at rest that are correlated with changes in repiration volume per time (**RVT**)). **e**) t-statistic of the difference in BOLD amplitude between left and right hemispheres before and after various calibrations. (Due to space considerations, only the results from the high contrast stimulus in the left visual vield (low contrast in the right visual field) are presented here. Similar results were obtained for the other order.