Subject-Specific BOLD fMRI Respiratory and Cardiac Response Functions Obtained from Global Signal

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Target audience: Researchers employed resting state fMRI and functional connectivity analysis to study brain functions. We propose a novel approach for performing single subject physiological noise correction to improve fMRI resting state and functional connectivity analyses.

Purpose: Slow changes in either breathing pattern or cardiac pulse rate alter BOLD fMRI. Such fluctuations are to a large extent not of neuronal origin and contribute to the physiological noise present in BOLD data. Methods for removing physiological noise have been proposed. One commonly used method, RVHR[1], employs both respiratory and cardiac template response functions (RRF, CRF). Both RRF and CRF templates are analytically described based on the average multi-subject data[1,2]. This approach does not account for intra-subject variations in physiological response. We propose a novel approach that employs subject-specific RRF and CRF obtained from the whole brain global signal (GS). Averaging multiple voxels in GS computation ensures physiological noise dominance over thermal/system noise in even high-spatial-resolution fMRI data, making GS suitable to derive robust estimation of both RRF and CRF for individual subjects. Our subject-specific approach explains more variance in the data without creating the problems caused by GS regression[3].

Fig.1

Methods: General Electric Discovery MR750 whole body 3T MRI scanner and a standard 8ch receive-only brain array coil were used for imaging. For fMRI, single-shot gradient-recalled EPI with SENSE (acceleration=2) was used. The imaging parameters were: TR/TE=2000/25ms; FOV/slice thickness=220/2.9mm; BW=250 kHz; flip angle=90°,60°, 30°, or 10°; 33 axial slices; matrix=128×128. Six healthy subjects underwent six fMRI resting scans during which they were asked to close their eyes and not fall asleep. The scan durations were 15, 15, 10, 10, 10, and 15 min for flip angles of 90°,90°,60°,30°,10°,and 90°, respectively. The results shown here are from the first ten minutes of runs 1, 2, and 6 (FA=90°). Physiological respiration waveforms and pulse oximetry were simultaneously recorded with the fMRI (40Hz bandwidth). _fMRI Preprocessing_: Data analyses were performed using AFNI and MATLAB. The preprocessing steps included slice timing correction, motion correction, removal of motion parameters and linear trends, smoothing (FWHM=5mm), and physiological noise correction using RETROICOR and RVT regressors prior to evaluations. The first 30 EPI volumes of each scan were also neglected. Fig. 1 shows the preprocessing steps in order. All aforementioned analyses were performed in subject's original space. However, to prepare final statistical results for group analysis, each subject's z-score

maps were transformed to Talairach space. **_RVHR_i_ Model:_** Deconvolving RV and HR simultaneously from the fMRI data (RVHR model) was proposed by Chang et al[1]. The model assumed that the time series of each voxel has been affected by temporal fluctuations of HR and RV through convolution of the CRF and the RRF, respectively. The RRF and CRF were deconvolved from each voxel time series and then the average over significant voxels for multiple subjects was fitted to an analytic CRF equation. The deconvolved RRF is similar to the analytical RRF proposed by Birn et al[2]. We propose a new approach for deriving individualized cardiac and respiratory response functions (RRF_i and CRF_i) using individuals' physiology recordings and GS. Removing physiological effects using analytical RRF or CRF may not be sufficient for all subjects, as some may not have similar physiological responses to respiration and cardiac changes. Using individualized response functions will aid in removing physiological noise from the data in an unbiased fashion. The new model, which will be referred to hereafter as $RVHR_i$, is constituted in the same structure as the RVHR model—the primary difference being that we deconvolved respiration and cardiac response functions from the GS. GS was computed by calculating average time series in the whole brain and RV and HR signals were derived using previous definitions[1].

Fig.3

Results: Fig. 2 shows RRF_i and CRF_i from the first two scans for 2 subjects. Fig. 3 illustrates full model R^2 for both RVHR and $RVHR_i$ models for a single subject (S1) in upper panel and group results along with the GS regression in the lower panel. Values were thresholded at $p < 0.001$. Fig. 3 clearly show the expansion of the explained variance in the brain when the individualized model was used, as compared to standard model, on both single and group levels. **_Functional connectivity analysis:_** The effect of the proposed physiological noise correction method on functional connectivity maps was investigated using a seed-based correlation analysis. The seed region ROI chosen was a 6mm-radius sphere in DMN (2L, 51P, 27S) in the Talairach space. These seed ROIs were then transformed to the subject's original space. Connectivity maps were generated by computing the correlation between the average time series in the seed ROI and all other voxels in the brain. See Fig. 4. Connectivity results indicate that physiological noise correction using the proposed individual filters instead of standard ones tend to decrease the positive correlation and increase the extent of negative correlations.

Discussion: We propose the use of subject-specific respiratory and cardiac response functions to better match an individual's physiological characteristics. Individualized RRF_i and CRF_i are derived from each subject's GS and external physiological measures to obtain robust physiological noise corrections for low-frequency BOLD fluctuations. The whole brain averaging to compute GS assures physiological noise dominance at various imaging parameters, including high-resolution scans. Physiological noise correction conducted on the same data set with the use of the subject-specific $RVHR_i$ model results in similar but expanded R^2 maps with larger number of voxels as compared to maps obtained after template RVHR correction. Expanding anti-correlation among different brain regions and also inducing correlations among regions without initial correlation are known issues caused by GS regression in functional connectivity analysis. Utilizing $RVHR_i$ physiological noise correction as an alternative in functional connectivity analysis results in more focal positive correlation and does not induce negative correlation to the data. Our novel approach effectively and robustly removes low frequency physiological noise for each subject.

Fig.4

Conclusion: We proposed a novel subject-specific approach for cardiac- and respiratory-related low-frequency physiological noise correction in BOLD fMRI data analysis. Instead of using analytical RRF and CRF derived based on multiple-subject averaging, individual subject-specific response functions are obtained from the BOLD global signal. Our approach improves BOLD physiological noise correction.

References: 1) Chang, C. et al., NeuroImage 2009, 44:857–869; 2) Birn, R. et al., NeuroImage 2008, 40: 644 – 654; 3) Murphy, K., et al., NeuroImage 2009, 44: 893-905.