Pain FMRI studies are improved by slice-wise removal of cardiac noise

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Introduction: Functional magnetic resonance imaging (FMRI) experiments employing painful stimulation are contaminated with physiologic noise as many cardiopulmonary parameters change significantly in response to pain [1]. Respiratory and cardiac contributions to physiologic noise differ in both the extent and magnitude of their effects, with respiration generally considered to have a more global effect [2]. In an abstract presented last year on FMRI of painful stimulation, implementation of a slice-by-slice correction for measured respiratory-induced noise improved model fit, eliminated false activations, and allowed detection of true activations previously masked by the noise [3]. Since noise due to cardiac pulsation has been shown to affect up to 27% of the voxels in the brain [4], a similar correction technique for cardiac noise should also improve the model, especially in pain studies. Previous approaches to reduce the effect of cardiac noise on the statistical analysis make assumptions about the frequency characteristics of the noise [2, 5, 6], but these conditions are likely to be violated in pain experiments. In this study, no assumptions are made about the length or variability of heart rate period. Rather, using data collected from cardiac monitoring, the actual effects of cardiac noise in FMRI of pain are removed from the data on a slice-by-slice basis.

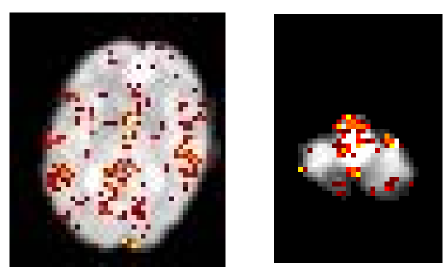
Methods: Seven healthy, right-handed subjects (4 male, aged 27 – 46, mean = 31 ± 6) were recruited in this Institutional Review Board approved FMRI study. For the functional task, painful transcutaneous electrical nerve stimulation (ENS) of the right index finger was used. Each pain epoch consisted of 30 seconds of painful stimulation followed by 30 seconds of rest. All images were collected on a 1.5 T General Electric (Milwaukee, WI) Signa scanner (GRE EPI, TR: 3 s, TE: 50 ms, flip angle: 90º, matrix: 64x64, FOV: 24 cm, in-plane resolution: 3.75x3.75 mm, slice thickness: 5 mm, 28 axial slices, 95 or 105 timepoints) in an interleaved fashion. The reconstructed images were corrected for gross subject motion, spatially smoothed, and temporally high-pass filtered before further processing. During scanning, a pulse plethysmograph (PPG) sensor was attached to the subject's left index finger and the PPG was recorded continuously along with the timing of the RF pulses from the scanner. The PPG dataset was low-pass filtered to remove high frequency noise from the gradients. Based on the timing of slice acquisition relative to the peaks of the PPG, each image's relative acquisition time within a beat-to-beat cardiac unit cycle was determined, as in [4]. These unit-cycle PPG data were regressed against the pre-processed image data for each slice independently, and the signal variance that correlated to the PPG waveform was subtracted from the data. Functional activation was then determined using general linear modeling (GLM) of the pain stimulus paradigm for both the PPG-corrected data and the initial uncorrected MR data. Adjusted coefficient of determination (R_a^2) values were calculated for each voxel from the residuals of model fitting to both data sets, allowing comparison of the analysis of the corrected and uncorrected data sets. For comparison with previously described methods of physiologic noise correction techniques, the change in the number of active voxels was also calculated.

Results: An image of the voxels containing significant cardiac noise for two slices of subject 6's data is displayed in Figure 1, with intensity of the overlay indicating the correlation of the MR signal at that voxel to cardiac noise. The distribution of contaminated voxels is typical of the other six subjects; the areas of greatest contamination are located near the basilar artery, the circle of Willis, and in areas near the middle cerebral arteries. The changes to the number of active voxels and to the maximum and mean R_a^2 values across all voxels are listed in Table 1. The mean R_a^2 across all voxels increased for all seven subjects when fitting the pain paradigm to the PPG-corrected dataset. The average increase in maximum R_a^2 was 34.6% and in mean R_a^2 was 23.0%, across all subjects. Although the number of activated voxels only decreased by an average of 4%, most subjects had clusters illustrating both increased and decreased numbers of active voxels after correction.

Table 1. Improvements in General Linear Model Fit after Cardiac Correction

Subject	Change in Active Voxels (%)	Max R_a^2 Increase (%)	Mean R_a^2 Increase (%)
1	-11.98	10.88	17.37
2	5.57	17.31	17.97
3	4.52	-1.80	14.66
4	0	32.28	29.28
5	-12.00	27.73	25.70
6	-15.86	27.38	30.89
7	12.75	128.18	25.17
Average	**-4.00**	**34.57**	**23.01**

Figure 1. Maps of Voxels Showing Significant Cardiac Noise in the Cerebellum and Cerebral Cortex of One Subject



Discussion: Dagli et al. [4] showed maps illustrating, for each image slice, the cardiac-correlated variation in scans collected by a multislice gradient echo EPI sequence. In addition to a re-demonstration of the localized cardiac noise distribution seen in [4], this work presents a method for removing cardiac noise from FMRI data, similar to that used for removing respiratory noise [3]. The improvement of fit to the GLM is proven by the increase in R_a^2. This measure of model fit only increases if the addition of the PPG parameter explains its share of the error from regression of the data (it is possible for R_a^2 to decrease when additional parameters are added to the model). Here we demonstrate that slice-by-slice correction of functional images using cardiac unit cycle data obtained with PPG monitoring improves the fit of subsequently applied linear modeling of the stimulus. This correction scheme removes both false positive and false negative voxels. The finding that, on average, the number of activated voxels decreased by 4% after correction, while the model fit improved by 23%, suggests that voxel counting is an inadequate means of comparing analysis methods.

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