Low-Frequency Fluctuations in the Cardiac Rate Contribute to Variance in the Resting-State fMRI BOLD Signal

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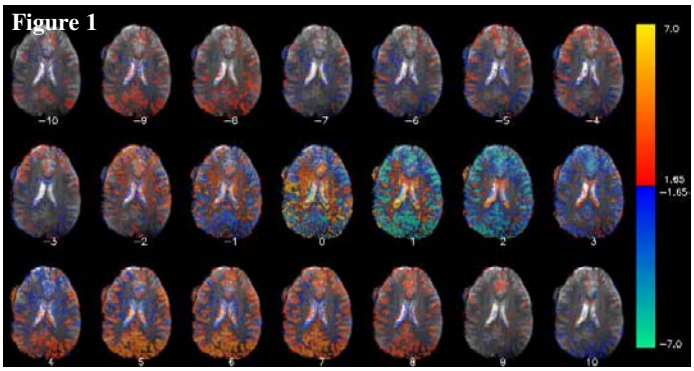
Introduction: Fluctuations in the cardiac rate (1-3) occur in the low frequency region (< 0.1 Hz) probed in resting-state functional connectivity studies and may therefore be linked to low-frequency BOLD signal fluctuations. Low-frequency oscillations in the heart rate and arterial blood pressure have also recently been found to account for about half of the information carried with low-frequency oscillations in the cerebral haemodynamics (4). To investigate the hypothesis that fluctuations in the cardiac rate and the BOLD signal may be related, temporal correlations between heart rate and resting-state fMRI signal timecourses were assessed.



Methods: Resting-state BOLD fMRI data were acquired using a 3T (GE) scanner equipped with a 16-channel head coil (Nova Medical) (single-shot GE-EPI, TE = 43 ms, TR = 6 s, 28 axial slices acquired in 3s, 1.7 x 1.7 x 3 mm^3, gap = 0.5 mm, 480 volumes). Heart beat and respiration were recorded with a standard finger-pulse-oximeter and respiratory bellows respectively. For each of 9 subjects, the cardiac rate timecourse was calculated from the trigger pulses output at every R-wave by taking the inverse of the beat-to-beat interval, rejecting non-physiological beat frequencies, smoothing (convolving with a Gaussian, FWHM ~ 3-beats) and resampling to yield a beat frequency for every 6 s TR period. Both the cardiac rate and voxel signal timecourses were identically detrended ($\leq 8^{th}$ order polynomials removed) and high-pass filtered ($\geq$ 0.005 Hz) to remove scanner drifts before calculating temporal cross-correlations over several time-lags in the Fourier domain. T-statistics of correlation were calculated, using the standard deviation (S.D.) of the covariances for all but the central 21 time-shifts (± 1 min). Gray and white matter (GM and WM) masks were obtained by thresholding maps of the correlation between voxel and 'global' timecourses.

Five nested regressions (see Table 1) were then carried out to investigate whether adding a few relevant lagged cardiac rate regressors to other well-known physiological noise regressors (5,6) would account for any additional variance in the signal. The resting-state fMRI BOLD signal has recently been found to be partially correlated with the respiration volume per unit time (RVT) (5) so 8 lagged RVT regressors were included in the full model. The combinations of regressors in the five models were chosen to allow comparison of the effect of adding in each set of physiological regressors. Five cardiac rate timecourses (shifted by 0 to 24s) were selected as regressors as these shifts yielded the largest correlation t-values (Fig 2). The adjusted coefficient of determination (R^2_{adj}) was calculated as a measure of the proportion of the MRI signal variance that could be explained by the regressors in each model.

Results: Several low-frequency components were present in the spectrum of cardiac rate variations (< 0.083 Hz). Significant correlations were found despite small variations in the cardiac rate (0.08 Hz average S.D. across subjects). T-maps of cardiac rate correlation for one slice in a single subject are shown for lags -10 to +10 TR (± 1 min) in Fig. 1. The mean GM and WM t-values averaged across all subjects are shown in Fig. 2. The strongest correlations were found in the GM, negative values at lags of 1-2 TR (6-12 s) and positive values at lags of 5-7 TR (30-42 s) of the MR signal behind the cardiac rate timecourse. The regression results are summarized in Table 1. Adding the cardiac rate regressors (C-B and E-D) explained as much additional variance as adding the RVT regressors (D-B and E-C). Although the cardiac rate and RVT timecourses were found to be significantly positively correlated, adding the cardiac rate regressors to other physiological regressors always explained substantial additional variance. As expected, the full regression model explained the most variance.

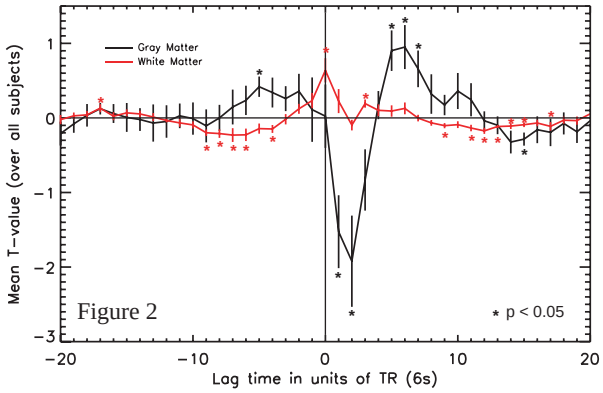


Table 1		Mean R^2_{adj} over whole brain	
Model	Regressors	Mean across subjects	SD across subjects
A	8 polynomial baseline	0.400	0.102
B	A + 8 RETROICOR	0.438	0.099
C	B + 5 lagged cardiac rate	0.452	0.093
D	B + 8 lagged RVT	0.454	0.091
E	D + 5 lagged cardiac rate (full model)	0.464	0.088

Discussion and Conclusions: Across-beat variations in the cardiac rate correlate with low-frequency fluctuations in the resting-state BOLD fMRI signal. The strongest correlations were found in the GM, perhaps due to its greater vascularisation, and not around the major vessels cf. (7), showing that the effects of cardiac rate fluctuations probed here are different from the direct effects of pulsatile cardiac motion observed in other studies. Regressors consisting of time-shifted cardiac rate timecourses explained additional signal variance in all subjects, even when used with other physiological regressors. Including these as 'nuisance variable' regressors can therefore be beneficial for fMRI studies and particularly important for resting-state functional connectivity studies based on low-frequency MRI signal fluctuations in the brain.

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