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Low Frequency Fluctuations in the Cardiac Rate as a Source of Variance in the Resting-State fMRI BOLD Signal

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Abstract

Heart rate fluctuations occur in the low frequency region (< 0.1 Hz) probed in functional magnetic resonance imaging (fMRI) studies of resting-state functional connectivity and most fMRI block paradigms, and may be related to low frequency blood-oxygenation-level-dependent (BOLD) signal fluctuations. To investigate this hypothesis, temporal correlations between cardiac rate and resting-state fMRI signal timecourses were assessed at 3 Tesla. Resting-state BOLD fMRI and accompanying physiological data were acquired and analyzed using cross-correlation and regression. Time-shifted cardiac rate timecourses were included as regressors in addition to established physiological regressors (RETROICOR (Glover et al., 2000) and respiration volume per unit time (Birn et al., 2006b)). Significant correlations between the cardiac rate and BOLD signal timecourses were revealed, particularly negative correlations in gray matter at time-shifts of 6–12 seconds and positive correlations at time shifts of 30–42 seconds ($TR = 6$ s). Regressors consisting of cardiac rate timecourses shifted by delays of between 0 and 24 seconds explained an additional 1 % of the BOLD signal variance on average over the whole brain across 9 subjects, a similar additional variance to that explained by respiration volume per unit time and RETROICOR regressors, even when used in combination with these other physiological regressors. This suggests that including such time-shifted cardiac rate regressors will be beneficial for explaining physiological noise variance and will thereby improve the statistical power in future task-based and resting-state fMRI studies.

Introduction

It is important to identify and characterize the sources of physiological noise in the blood-oxygenation-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) signal so that noise reduction strategies can be developed and improved. This is especially relevant as technical advances, such as the use of higher magnetic fields or multiple receiver coils, have increased the available MRI signal. Physiological noise depends on the total signal strength and therefore becomes a larger fraction of the total noise as the signal increases (Kruger and Glover, 2001; Kruger et al., 2001; Triantafyllou et al., 2005), for example with increased magnetic field strength.

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Physiological noise negatively affects conventional task-based fMRI experiments and has been found to be particularly problematic in the absence of external stimuli, in resting-state functional connectivity analysis (Cordes et al., 2001). In this type of analysis neuronal connections between brain regions are inferred by measuring the spatial correlations of low frequency (< 0.1 Hz) BOLD fMRI signal fluctuations in the brain. The minimization of physiological noise as a confound in such studies has been a preoccupation since their inception (Biswal et al., 1996; Fukunaga et al., 2006b; Lowe and Sakaie, 2006; Vogt et al., 2006).

Several physiological noise sources have been identified, including effects related to the cardiac (Bhattacharyya and Lowe, 2004; Dagli et al., 1999) and respiratory (Birn et al., 2006b; Wise et al., 2004) cycles. Variations related to arterial carbon dioxide fluctuations (Wise et al., 2004) and residual movement artifacts not accounted for by rigid body registration (Lund et al., 2005) also contribute.

Various methods for reducing physiological noise have been proposed. These may operate in k-space (Hu et al., 1995; Le and Hu, 1996; Wowk et al., 1997) or in image space (Chuang and Chen, 2001; Deckers et al., 2006; Glover et al., 2000) with the latter being the preferred method since changes made in k-space affect all the voxels in the reconstructed images. This makes spatially localized noise difficult to remove and may induce spatial correlations. Fixed bandwidth band-reject filtering was initially proposed (Biswal et al., 1996) to remove noise at the fundamental cardiac and respiratory frequencies but can only be applied successfully when variations at these frequencies are stationary and adequately sampled (as in the rare case of imaging with very short TR) so that they are not aliased to lower frequencies. Moreover, such filtering cannot be applied if task-related signals are present in the rejected frequency band.

Some noise-reduction methods involve the acquisition of additional physiological data (Glover et al., 2000; Hu et al., 1995; Liston et al., 2006; Vogt et al., 2006) using a photoplethysmograph and pneumatic belt, for example. Other methods utilize the MRI data itself to estimate the noise (Le and Hu, 1996; Lowe and Sakaie, 2006; Wowk et al., 1997). Some of the methods are designed for straightforward data correction (Glover et al., 2000) but most can be extended to perform 'nuisance variable regression' (Birn et al., 2006a; Lund et al., 2006) in which the physiological noise measures (or models derived from them) are included as regressors in a general linear model (GLM) regression analysis. This regression method is advantageous over applying a filter or additional data correction as it does not interfere with the detection of functional activation (Deckers et al., 2006).

Many studies have demonstrated that there are fMRI signal changes associated with the pulsatile cardiac motion (both at the cardiac frequency and its harmonics) (Bhattacharyya and Lowe, 2004; Biswal et al., 1996; Dagli et al., 1999; Kruger and Glover, 2001). Most of the physiological noise reduction methods model the contribution from the cardiac motion by determining the relative timing of each image volume (or slice (Liston et al., 2006; Vogt et al., 2006)) within the cardiac cycle. They assume that the cardiac cycle follows the same inherent pattern regardless of the inter-beat time interval. This assumption is not entirely accurate as there are differences in the time interval between beats that are associated more with time variation in the diastolic portion of the cardiac cycle than the systolic (Dagli et al., 1999).

Across-beat fluctuations in the heart rate have been found to occur in several frequency bands (Akselrod et al., 1981; Cohen and Taylor, 2002; Otzenberger et al., 1998) including the low frequency region investigated in fMRI studies of resting-state functional connectivity (< 0.1 Hz). In fact, a recent study suggests that systemic cardiovascular fluctuations (low frequency oscillations in the heart rate and arterial blood pressure) can account for about half of the information carried with low frequency oscillations in the cerebral haemodynamics (specifically in the oxyhaemoglobin concentration change) (Katura et al., 2006). Fluctuations

in the heart rate may therefore be related to those in the BOLD fMRI signal, particularly since the signal is dependent on the cerebral blood flow, oxygenation and volume. Furthermore, since respiration and the cardiac rate are intimately related (Cohen and Taylor, 2002) and the respiration volume per unit time (RVT) has recently been found to be correlated with the resting-state fMRI BOLD signal (Birn et al., 2006b), it is probable that fluctuations in the cardiac rate are related to those in the resting-state fMRI BOLD signal. The effect of cardiac rate fluctuations on the fMRI signal have not been assessed or explicitly accounted for in physiological noise models.

Therefore, the aim of this study was to investigate the hypothesis that across-beat fluctuations in the cardiac rate are correlated with low frequency variations in the resting-state BOLD fMRI signal. Temporal and spatial patterns of fMRI signal changes related to variations in the cardiac rate were characterized. To this end, resting-state BOLD fMRI data and accompanying physiological data were acquired and analyzed using both cross-correlation and regression. Subsequent to and informed by the cross-correlation analysis, several nested regression analyses were performed to determine whether adding a set of time-shifted cardiac rate timecourses to other established physiological noise regressors would explain additional variance in the data.

Methods

Imaging

Resting-state BOLD fMRI data were acquired using a 3 Tesla scanner (GE Signa, Milwaukee, WI, USA) equipped with a 16-channel head coil (Nova Medical, Wakefield, MA) (de Zwart et al., 2004). The imaging sequence, developed in-house, was a single-shot gradient-echo EPI with TE = 43 ms and TR = 6 s with all the slices acquired during the first three seconds of the TR interval, leaving a quiet period in which EEG acquisition could take place (Horovitz et al., 2006, Horovitz et al., in press). In each volume, 28 axial, 3 mm-thick slices were acquired sequentially with a slice gap of 0.5 mm. The in-plane image resolution was $1.7 \times 1.7 \text{ mm}^2$. After one minute, subjects were instructed to close their eyes and allowed to fall asleep. A total of 480 volumes were acquired with the subjects in this resting state, corresponding to an imaging time of 48 minutes. A visual task was presented for the final ten minutes of each study but the segments of each timecourse associated with this visual paradigm presentation were not included in the analysis presented here.

The first five image volumes (and corresponding timepoints in the cardiac and respiratory data) were discarded prior to correlation or regression analyses in order to ensure that the spins had reached a steady state. Motion correction was performed by rigid-body registration of every image volume to the penultimate volume of each timecourse (Thevenaz et al., 1995; Unser et al., 1993). The analysis was performed using IDL 6.2 (ITT visual information solutions, Boulder, CO, USA) with some use of AFNI software (<http://afni.nimh.nih.gov/afni/>) for the image registration prior to the regression analysis. The EEG and fMRI data were analyzed separately for studies of resting-state functional connectivity (Fukunaga et al., 2006a; Horovitz et al., 2006).

Physiological Data Acquisition

The subjects' heart beats were recorded using a photoplethysmograph placed on the left index finger. Respiratory data were acquired using a respiratory belt placed around the chest. Both are standard equipment on the GE scanner. The scanner provided a TTL pulse output for each heart beat as well as a scaled respiratory waveform. Both these physiological signals were sampled at a rate of 1 kHz using a Windows PC running in-house software. Scanner trigger

pulses, output at the start of each imaging volume, were also acquired to allow accurate synchronization of physiological signals with the fMRI data.

A total of fourteen subjects were scanned in twenty-two study sessions according to the protocol described above. All subjects gave written informed consent according to a protocol approved by the Institutional Intramural Research Board (IRB). Ear-plugs were provided for hearing protection. The scanner's peak-detection software output a TTL pulse every time it detected a peak in the photoplethysmograph signal. The peak-detection was verified in a separate experiment in our laboratory (with simultaneous ECG acquisition) and was found to reproducibly provide a TTL pulse 120 ms after the ECG R-wave, with a standard deviation in the TTL pulse timing of 25 ms over approximately two hours and fifteen minutes. However, in some sessions, the scanner's peak-detection software detected too many pulses or failed to detect pulses for long periods. Such un-physiological 'spurious' pulses may have arisen due to baseline shifts or gain changes in the photoplethysmograph signal or due to the subject moving their fingers or a having a very weak finger pulse. When greater than 5% of the beats detected were spurious, the quality of the cardiac data was regarded as too poor to allow a meaningful beat-to-beat measure of the cardiac rate to be calculated and the session was excluded from further analysis. In addition, two sessions were excluded for having severely ghosted images, leaving data from twelve sessions, nine subjects (3 females, 6 males, age range: 23 to 39 years, average age: 30 years) to be analyzed in this study. The sessions included in the analysis had less than 2 % spurious cardiac beats.

Data Analysis

After extracting the cardiac rate information from the raw physiological data, two stages of analysis were performed, firstly a temporal cross-correlation analysis followed by a more detailed regression analysis. The aim of the correlation analysis was to detect correlations for several relative temporal shifts between the cardiac rate and the resting-state fMRI signal. The correlations and their temporal behaviour in the gray and white matter were then compared. Finally, several nested regressions were performed to determine whether inclusion of cardiac rate regressors at a few relevant lags would give additional explanatory power, and therefore be useful for reducing physiological noise, when used in addition to other physiological noise regressors. As a control, the correlation and regression analyses were repeated, substituting a simulated randomly fluctuating cardiac rate for the measured heart rate.

Extracting the Cardiac Rate—The raw cardiac 'trace' consisted of square TTL trigger pulses, output by the scanner every time it detected a peak in the photoplethysmograph signal. The steps in extracting the cardiac rate are illustrated in Figure 1. The beat-to-beat interval was calculated and the inverse of each interval was designated as the beat-to-beat cardiac rate. In other words, the TTL pulse at each beat was replaced with the inverse of the time from that beat to the next as shown in Figure 1a. As described above, there were a few (< 2%) spurious beat frequencies that were far too slow or too fast to be physiological. These spurious beat frequencies were removed by rejecting any beat frequencies that were more than 1.7 standard deviations (calculated across the whole timecourse) away from the local median (in a 6 s time window) and replacing them with the mean of the two nearest non-spurious beat frequencies. The effect of this is illustrated in Figure 1b. The resulting 'clean' cardiac rate timecourse was then smoothed further by convolution with a Gaussian window ($\sigma = 1$ beat, total width = 15 beats) to remove any remaining high-frequency noise and ensure that the timepoints (beats) selected by the subsequent resampling would have rates representative of the surrounding 6 s TR period. The effect of the smoothing on the cardiac rate timecourse and spectrum is shown in Figures 1c and d respectively. The smoothed cardiac rate timecourse was then resampled (see Figure 1e) by selecting the heart rate timepoint (beat) in each 6 s TR period nearest to the

MRI scanner trigger pulse output at the beginning of that TR. This yielded a cardiac rate timecourse with one timepoint for every image volume rather than at every heartbeat.

Cross-Correlation Analysis—A correlation analysis was performed to look for any temporal correlations between the cardiac rate and the resting-state fMRI signal.

Both the cardiac rate and each voxel signal timecourse were identically de-trended and filtered prior to the correlation analysis to remove any ultra-low frequency drifts due to hardware instabilities. The de-trending involved fitting and removal of polynomials (Worsley et al., 2002) up to eighth order and the filter was a high-pass filter with a cutoff at 0.005 Hz and a cosine transition width of 0.002 Hz. It should be noted that the bandwidth of the cardiac rate variation data is ± 0.083 Hz (because of the 6s TR).

The temporal cross-correlations between the cardiac rate variation and the resting-state fMRI signal in each voxel were subsequently calculated in the Fourier domain using the cross-correlation theorem. Calculating the cross-correlations in the Fourier domain yielded results for all possible temporal shifts (both positive and negative) of the cardiac rate relative to the image data in one step. However it should be noted that for very large shifts, these results do not reflect an accurate cross-correlation since the Fourier method assumes periodicity of the data beyond the measurement time-window.

Correlation coefficients and t-statistics of correlation were calculated from the resulting covariance values. The t-value for each lag was calculated by dividing the covariance value for that lag by the standard deviation of the covariances across all lags except for the central 21 lags (delays -10 to +10 TR). This is because any significant correlations were expected to occur within the central 21 lags (± 1 minute) of the imaging data relative to the cardiac data. Covariances calculated for greater time shifts could therefore be used as estimates of 'noise'. T-maps were produced using a t-threshold of 1.65, corresponding to an uncorrected p-value of 0.05.

A cerebro-spinal fluid (CSF) mask was obtained by thresholding (at approximately 15% of the maximum image intensity) the difference image derived from the first two image volumes. CSF is bright in the difference image since it has the longest T_1 of all the tissues and the CSF signal is not fully relaxed after the first TR, before the second image excitation. The CSF mask was used to exclude CSF from the gray and white matter masks generated as described below.

A gray-white matter segmentation was based on the correlation between the 'global' signal timecourse and the signal timecourse in every voxel (Birn et al., 2006a). The global signal was obtained by averaging the signal in all the voxels inside the brain (of which a mask was obtained using FSL BET (<http://www.fmrib.ox.ac.uk/fsl/bet/index.html> (Smith, 2002)) to skull-strip the first EPI image) at every timepoint. Before correlation, both timecourses were de-trended by removing polynomials up to eighth order. The temporal cross-correlation of the timecourses was calculated (at zero time shift) and two thresholds were selected: one above which the resulting mask contained mostly gray matter (GM) and another threshold below which the resulting mask contained mostly white matter (WM). This method was used because simply thresholding the EPI images at a particular intensity value did not give accurate or consistent separation of GM and WM since the contrast between these tissues is not optimal in T_2^* -weighted EPI for fMRI. In addition, the signal intensity across the images varied due to susceptibility-induced distortion and drop-out, B_1 inhomogeneity and the non-uniform sensitivity profile of the 16-channel receive-only coil. The mean t-values for the covariance of the cardiac rate and MRI signal were calculated inside the GM mask and the WM mask at every time shift.

For lags between -10 to +10 TR these mean GM and WM t-values were then averaged across all 9 subjects (1 session per subject). A further t-test, using the standard error of the mean, was performed to test the significance of these averaged values at the 5% level (two-tailed).

Maps were created showing the maximum (positive or negative) correlation coefficient over lags of -10 to +10 TR (± 1 minute). Corresponding lag histograms of this data were also plotted, showing the lags at which these maximum correlation coefficients occurred.

As well as the voxel-by-voxel correlations described above, some ‘global’ cross-correlations were performed using the same method but correlating the cardiac rate with the timecourse of the global mean signal in the whole brain, the timecourse of the mean signal in the GM and the timecourse of the mean signal in the WM. This was done in order to determine whether a single ‘global’ detrending might be applied to such data in future.

A repeat of the correlation analysis for one subject without filtering the data gave almost identical results and indicates that the filtering is probably redundant and does not need to be used in addition to de-trending with polynomials up to eighth order in future correlation analyses. For this reason, only de-trending (using the 8 polynomials as baseline regressors), without filtering, was performed in the regression analyses described below.

To determine whether any correlations between the cardiac rate and signal timecourses were consistent across subjects, group maps of pooled t-statistics were created from the individual t-maps of the correlation from 8 subjects (one t-map per subject, see Table 1). One subject (H in Table 1) was excluded from the group analysis since spatial normalization of her brain did not yield a satisfactory match with the template. The excluded subject’s raw brain echo-planar images had some small areas of signal drop-out (and geometric distortion) in parts of the cortex in some superior slices. These could have been artifacts, caused perhaps by material in the subject’s hair, or normal anatomical variation. Irrespective of their cause, the regions of drop-out caused the spatial transformation into the standard space to fail severely, as judged by visual inspection. Matrices for spatially transforming each individual brain into the standard Montreal Neurological Institute (MNI) space were calculated by co-registering a single EPI volume from each subject with the SPM (<http://www.fil.ion.ucl.ac.uk/spm/>) EPI MNI template using a linear affine transformation method with 12 parameters (FSL FLIRT <http://www.fmrib.ox.ac.uk/fsl/flirt/> (Jenkinson and Smith, 2001)). The t-maps of correlation for each individual were then transformed using the calculated matrices with sinc interpolation. The transformed maps were smoothed by convolution with a Gaussian kernel of size $4 \times 4 \times 2$ voxels. A voxel-based t-test was then carried out to test whether the mean t-value over all the subjects was significantly different from zero, using a pooled standard deviation over all voxels (Jansma et al., 2001).

Regression Analysis—A set of five nested regressions was carried out to investigate whether adding a few relevant lagged cardiac rate regressors to other well-known physiological noise regressors would be able to explain additional variance in the data. This was a necessary test since it might be possible that the cardiac rate regressors are strongly correlated with some of the other physiological noise regressors, in which case including the cardiac regressors would not be expected to give much extra information about the data.

The cardiac rate regressors were created by shifting the final resampled cardiac rate timecourse (extracted as explained above) in time relative to the imaging data. A subset of 5 lagged cardiac rate regressors (delays of 0 to 4 TR or 0 to 24 s) were selected as potentially more relevant on the basis of the correlation analysis since the largest correlation coefficients in the GM were found within these time shifts.

All the models included 8 baseline regressors which were polynomials up to eighth order intended to remove any very low frequency drifts. The other physiological noise regressors used were 8 RETROICOR (Glover et al., 2000) regressors (4 based on the cardiac phase and 4 on the respiratory phase, up to the second order terms) and 8 lagged respiration volume per unit time (RVT) regressors. These last 8 RVT regressors were created from the full respiratory bellows trace following the published method (maximum - minimum / inter-peak time) (Birn et al., 2006b) but the data were interpolated to only one point for every TR rather than the finer time interpolation used by Birn et al. Shifts of a whole number of TR were also used to generate the delayed RVT regressors (rather than shifts of 0.5 s) to minimize the number of regressors in the full model and since the fine temporal behaviour had already been investigated in detail (Birn et al., 2006b). Eight shifts of the RVT timecourses (from -2 to +5 TR) were chosen based on the published latencies of the resting-state fMRI signal response (Birn et al., 2006b).

The five nested regression models (see Table 2) were chosen such that the explanatory power of each set of regressors relative to that of the other sets could be assessed by comparing the results of the different regression models. For example, the results of the regression with model 5 can be compared to the results of the regression with model 4 to reveal whether including the set of lagged cardiac regressors explains additional variance in the data.

For each of the regression models, the adjusted coefficient of determination (R_{adj}^2), which has values between 0 and 1, was calculated as a measure of the proportion of the MRI signal variance that could be explained by the regressors in each model. The adjusted R^2 is so-called since it is adjusted to remove the effect of increasing the total number of regressors in the model. To indicate whether the 5 cardiac rate regressors were useful in explaining additional physiological noise in the data, the R_{adj}^2 values for each model were compared by subtraction.

Maps of the successive differences in R_{adj}^2 (ΔR_{adj}^2) between the models were calculated as follows: model 2 – model 1 ($\Delta R_{adj, 2-1}^2$), $\Delta R_{adj, 3-2}^2$, $\Delta R_{adj, 4-2}^2$, $\Delta R_{adj, 5-4}^2$, $\Delta R_{adj, 5-3}^2$, and $\Delta R_{adj, 5-1}^2$. The mean of each of these ΔR_{adj}^2 quantities over the whole brain was calculated for each subject. The mean and standard deviation over all the subjects were then also calculated.

These differences were chosen as they are expected to reveal the most about the regressors of interest. For example, $\Delta R_{adj, 2-1}^2$ would be expected to be large and positive if adding in the 8 RETROICOR regressors explains much more of the variance in the data than the 8 baseline regressors alone. The specific hypothesis here was that $\Delta R_{adj, 5-4}^2$ would be positive, suggesting that adding the 5 lagged cardiac rate regressors to a regression model including all the other physiological noise regressors would explain some additional variance in the MRI signal.

The five cardiac lags selected for use in the regression analysis may not necessarily be the optimal subset of lags to explain the signal variance. In order to investigate which subset of lags is optimal it would be necessary to perform nested regression analyses involving all possible permutations of, say, the lags from -10 to +10 TR (-60 to +60 s) to see which subset of lags gave the largest R_{adj}^2 . As an indication of the relative relevance of the subset of five cardiac lags selected, three nested regression analyses were performed, one including the 8 polynomial baseline regressors, a second including the baseline regressors and the 5 lagged cardiac rate regressors included in models 3 and 5 above (lags from 0 to 4 TR (0 to 24 s)), and a third including the baseline regressors and 21 lagged cardiac rate regressors (lags from -10

to + 10 TR (-60 to +60 s)). Adjusted R^2 (R_{adj}^2) statistics were calculated for each model as described for the 5-model nested regression analysis above.

As stated above, it might be possible that the cardiac rate regressors are strongly correlated with some of the other physiological noise regressors. For this reason, the cross correlation coefficient between the RVT and cardiac rate timecourses was calculated for each subject (using the Fourier transform method described above for the cross-correlation analysis).

Simulated Cardiac Rate—As a control and to serve as an assessment of the null hypothesis expectations from the analyses described above, they were repeated with a simulated cardiac rate. A randomly fluctuating heart rate timecourse was simulated by synthesizing square pulses with a constant spacing of 971 ms (equal to 1/the mean heart rate across all the subjects (see Table 1)) and adding a random ‘jitter’ from a Gaussian distribution with a variance of 78 ms (equivalent to the mean standard deviation in the heart rate over all the subjects (see Table 1)). The simulated heart rate timecourse was then processed with exactly the same steps as for extracting the real heart rate timecourse (Figure 1). The correlation and regression analyses were carried out exactly as described above but this time substituting the simulated heart rate timecourse for the measured heart rate timecourse for each subject.

Results

The mean and standard deviation of the cardiac rate for each session and averaged across all the sessions are given in Table 1.

Figure 2 illustrates the Fourier transform of the resampled cardiac rate timecourse, averaged over all subjects. The figure shows that most of the variations in the heart rate occur at very low frequencies (< 0.1 Hz) and that there are no distinct frequency peaks in the spectrum of cardiac rate variations. This was found to be the case for all the subjects.

Results of Cross-Correlation Analysis

Despite the fact that the fluctuations in cardiac rate were small (i.e. refer to the small standard deviations in Table 1), the correlation analysis yielded relatively strong correlations in some subjects. Mean cardiac rate – BOLD signal correlation coefficients in the GM and WM for all sessions are given in Table 1 for a lag time of 2 TR since the strongest correlations were found in the GM at this lag time (see Figure 5). The lag of 2 TR corresponds to the MR signal timecourse lagging 12 seconds behind the cardiac rate timecourse. T-maps of the cardiac rate-fMRI signal correlation for a single subject with strong correlations are shown in a single slice for lags -10 to +10 TR (± 1 minute) in Figure 3 a and in several slices at a lag of 2 TR (12 s) in Figure 4 a. Accompanying correlation maps for the simulated cardiac rate in the same subject are shown in Figures 3 b and 4 b and these demonstrate that the correlations found between the simulated cardiac rate and the resting-state fMRI signal were extremely weak relative to those with the measured cardiac rate.

Figures 3 a and 4 a demonstrate that the strongest correlations in this subject are located mostly in cortical GM regions and are negative correlations occurring at shifts of 6 s and 12 s respectively. Some reasonably strong positive correlations are also found in the GM at lag times of 5 to 7 TR (30 to 42 s). There are also a few areas of strong positive correlation in and around the ventricles at lags of 0 to 1 TR. The WM seems to have very few supra-threshold voxels except at lags -1 to 1 TR (± 6 s) where some positive correlations appear.

The averaged t-statistics in the GM and WM masks from two scanning sessions for a strongly correlating subject are illustrated in Figures 5 a and b. These figures show strong inter-subject

reproducibility and that the GM has greater t-scores than the WM. The mean GM t-value for all subjects is shown in Figure 5 c and the average across all subjects is shown in Figure 5 d. In both Figures 5 c and d only one scanning session is included per subject. In Figure 5 e the averaged t-statistics of correlation with the simulated cardiac rate timecourse are shown for the same subject and scanning session as in Figure 5 b.

Figures 5 (a-d) show that, across all nine subjects, the strongest correlations between the measured cardiac rate variation and the resting-state BOLD signal were found in the GM for relative time shifts of around 1 to 2 TR (or 6 to 12 s). Figures 3 a, 4 a and 5 also demonstrate that the GM voxels generally show a stronger overall correlation than those in the WM and this was observed in all the studies. As demonstrated in Figure 5 (a-d), there appears to be, in most subjects, a specific temporal pattern of correlation within the GM; a strong negative correlation at early lags, followed by a weaker positive correlation over several lags. There was no discernible temporal pattern of correlation between the simulated cardiac rate data and the resting-state fMRI signal as illustrated in Figure 5 e.

Figure 6 shows that the largest correlation coefficients for shifts between ± 10 TR for the subject shown in Figures 3-4 were negative and found mainly in the GM. This figure emphasizes the findings from Figures 3, 4 and 5, that the GM had stronger overall correlations than the WM (which had some positive correlations) and that the negative correlation coefficients in the GM were larger than the positive correlation coefficients.

A lag histogram corresponding to Figure 6 is shown in Figure 7 a. It shows the lags between ± 10 TR at which voxels in the brain have the largest correlation coefficients between the measured heart rate and the resting-state BOLD signal and emphasizes the temporal patterns illustrated in Figures 3 a and 5 a-d, with the strongest correlations in the brain occurring at lags 0-2 TR (0-12 s). A lag histogram for correlations of the same subject's MRI data with the simulated cardiac rate timecourse is shown in Figure 7 b which has no clustering of the strongest correlations around a group of early lags.

The 'global' correlations (not shown) of the mean signal timecourses in the GM and WM with the measured cardiac rate timecourses showed very similar temporal patterns to the mean voxel-by-voxel correlations illustrated in Figure 5 d. The behaviour of the whole-brain 'global' correlation was almost identical to that of the GM.

The results of the group analysis are displayed in Figure 8. Strongly-correlated regions included occipital (visual) cortex, posterior cingulate, parietal and frontal regions. As observed for the individual subjects, the regions with the most significant correlations across the group are mostly found in the GM. There is substantial overlap between the areas having the strongest negative correlations at lags 1 and 2 TR (6 to 12 s) and those regions with strong positive correlations at lags 5 and 6 TR (30 to 36 s). The temporal behaviour, over lags -20 to +20 TR (± 2 min), of the mean group pooled t-statistics, within a mask of the supra-threshold voxels ($p < 0.001$) at lags 1 and 2, was almost identical to the temporal behaviour of the mean in a mask of the supra-threshold voxels at lags 5 and 6 and to the GM plot in Figure 5 d.

Results of Regression Analyses

The results of the 5 nested regression analyses are summarized in Table 2 and illustrated in Figure 9. For example, the mean value and map (Fig. 9 d) of $\Delta R_{adj,5-4}^2$ illustrates the effect of adding the 5 lagged cardiac rate regressors to model 4. The continued increase in the mean R_{adj}^2 values as each set of regressors was added into the model shows that these additional regressors were useful in explaining variance in the data. Adding the cardiac rate regressors derived from the measured timecourses explained additional variance in all the subjects.

Adding the measured cardiac rate regressors to model 2 ($\Delta R_{adj,3-2}^2$) explained as much additional variance as adding the RVT regressors ($\Delta R_{adj,4-2}^2$). Both the cardiac rate ($\Delta R_{adj,5-4}^2$) and RVT ($\Delta R_{adj,5-3}^2$) regressors explained a similar additional variance when included with the other set in the full model, although this was smaller than the additional variance explained when first adding in each set of regressors without the other (i.e. $\Delta R_{adj,5-4}^2 < \Delta R_{adj,3-2}^2$ and $\Delta R_{adj,5-3}^2 < \Delta R_{adj,4-2}^2$).

The 8 baseline regressors explained the most variance in the MRI signal although adding each set of physiological regressors explained more variance (i.e. lead to incremental increases in the ΔR_{adj}^2 values in Table 2) up to a maximum value of 0.46 ± 0.09 for the full model 5. The effect of adding in the 8 RETROICOR regressors was the greatest out of all the sets of physiological regressors, having the highest mean ΔR_{adj}^2 value in Table 2 and the brightest images in Figure 9 (Figure 9 a compared to Figs 9 b-e).

The results of the regression analyses including simulated cardiac rate timecourses as regressors instead of the real measured cardiac rate timecourses are shown in Table 3. The effect of adding in 5 lagged randomly fluctuating simulated cardiac rate regressors is negligible (or even slightly detrimental), as can be seen by the zero (negative) values of $\Delta R_{adj,3-2}^2$ and $\Delta R_{adj,5-4}^2$ in Table 3. These results show that, unlike the measured cardiac rate regressors, the simulated cardiac rate regressors do not explain any variance in the MRI data.

The results of the three nested regressions involving only lagged measured cardiac rate timecourses are shown in Table 4. The 5 lagged cardiac rate regressors used in the main regression analysis explained 66 % of the additional variance explained by adding in all 21 lagged cardiac regressors.

The across-subject mean correlation coefficient (maximum across all lags for each subject) between the RVT and the cardiac rate timecourses was 0.28 ± 0.10 ($p < 0.0001$). The maximum correlation coefficients for each subject occurred at a lag of the cardiac rate of 0 or 1 TR (6 s) behind the RVT.

Discussion and Conclusions

Both the correlation and regression analyses performed here revealed significant correlations between the cardiac rate and resting-state fMRI signal timecourses, particularly in the GM which showed the strongest negative correlations at time shifts of around 6-12 seconds and large positive correlations at time shifts of 30-42 seconds. Regressors consisting of time-shifted measured cardiac rate timecourses explained substantial additional MRI signal variance when included in a model with other established physiological regressors. In contrast, substituting a simulated randomly fluctuating cardiac rate into the correlation and regression analyses gave negligible correlations and did not explain any variance in the data.

The across-subject mean cardiac rate and average standard deviation (see Table 1) are very similar to the values measured by Dagli et al in their study (Dagli et al., 1999) of the effects on fMRI of cardiac pulsatility in six healthy volunteers i.e. 60 ± 5 beats per minute with an average standard deviation of approximately 6%. As found in other physiological studies involving heart rate variability (Akselrod et al., 1981; Cohen and Taylor, 2002; Otzenberger et al., 1998), the spectra of measured cardiac rates variations (Figure 2) was greatest at the low frequencies (< 0.1 Hz) probed in this study, but with no distinct frequency peaks. This low frequency region contains both the BOLD fMRI signal fluctuations associated with functional

connectivity and the stimulus frequencies for most block-design fMRI paradigms. Any correlations found here between fluctuations in the cardiac rate and the fMRI signal would therefore suggest that variations in the cardiac rate may affect both of these types of fMRI experiments.

The results indicate that GM shows stronger overall MRI signal correlations with the cardiac rate timecourse than the WM, as emphasized by the dark-highlighted GM in the maps of the maximum correlation coefficient (Figure 6) and the group maps (Figure 8). This is as expected since the GM is more highly vascularized than the WM, giving greater BOLD signal and fluctuations. This may also explain why even the very weak correlations with the simulated cardiac rate timecourse seem stronger in the GM (see Figures 3 b, 4 b and 5 e) (i.e. this may be because the noise in the fMRI signal in the GM is greater than in the WM). The weak correlations with the simulated cardiac rate timecourse occasionally appear to cluster, for example in the visual cortex (see Figure 4 b). This is a manifestation of the well-known phenomenon of spatial autocorrelation in resting-state BOLD fMRI data (Biswal et al., 1995; Horovitz et al., in press; Fukunaga et al., 2006b).

The significantly correlating regions highlighted in the group maps (Figure 8) include regions, such as the posterior cingulate, medial frontal and angular gyrus that are commonly included in the default mode network (Raichle et al., 2001) and are typically deactivated during task performance, as well as frontal regions and regions in the visual cortex, that show increased activity during tasks. There does appear to be overlap between the regions highlighted in this study and those regions found to correlate strongly with the respiration-volume-per-unit-time (RVT) (Birn et al., 2006b). For example, the occipital and posterior cingulate areas were found to be significantly correlated with both the cardiac rate (Fig 8) and the RVT (Birn et al., 2006b).

The bright areas in Figures 9 b and d, in which the additional variance explained by the cardiac rate regressors is greatest, are similar to the areas that have the strongest correlations with the cardiac rate (Figures 3, 4, 6 and 8) as expected.

The regions found here to be highly correlated with the cardiac rate are not particularly concentrated around large vessels (although it should be noted that the data in the lower slices in which many of the vessels are found had significant EPI susceptibility-induced distortions and drop-outs). This is in contrast with previous studies (Birn et al., 2006a; Dagli et al., 1999; Glover et al., 2000; Liston et al., 2006; Vogt et al., 2006) in which the effects of the pulsatile cardiac motion on the BOLD fMRI signal have been found to be strongest close to the major vessels and their main branches. The fact that the regions revealed in this study are different demonstrates that the effects of across-beat variations in the cardiac rate probed here are different from the direct effects of the pulsatile cardiac motion observed in other studies. This is corroborated by Figure 9 in which the additional variance explained by the RETROICOR regressors (Fig 9 a) is located near the vessels and in the CSF and does not generally overlap with the regions in which the lagged cardiac regressors explain the most additional variance (Fig 9 b and d).

As well as revealing the spatial patterns of correlations, performing the correlation and regression analyses over several time delays allowed temporal patterns to be investigated. The strongest correlations between the cardiac rate and BOLD timecourses in GM (Figures 5 a-d) occurred between time delays of 0 and 4 TR (0 to 24 s) (Figure 7 a). For this reason, these early lags were selected for the subsequent regression analyses. This temporal behaviour is very different from that of the correlations with the simulated cardiac rate (Figures 3 b, 5 e and 7 b). For example the lag histogram in Figure 7 b is similar to a noisy uniform distribution,

showing that voxels in the brain seem almost equally likely to have a maximum correlation at any lag, as expected if correlations with the simulated heart rate arise by chance.

Changing the regressors in the model gives an indication of the signal variance that can be equivalently explained by different regressors. For example, comparing the results of regression model 3 with the results of the full regression (model 5 in Table 2), it appears that when adding in the 5 lagged cardiac rate regressors without the RVT regressors, they explain more additional variance than when they are added in with the RVT regressors. Therefore there is some signal variance ($0.5\% = \Delta R_{\text{adj},3-2}^2 - \Delta R_{\text{adj},5-4}^2 \approx \Delta R_{\text{adj},4-2}^2 - \Delta R_{\text{adj},5-3}^2$) that can be equally well explained by either the cardiac rate or the RVT regressors. This is reflected in the correlation between the RVT and the cardiac rate regressors.

Despite this, the cardiac rate and the RVT regressors each still explain additional variance that is not explained by the other set of regressors, as evidenced by the additional 1 % variance explained by adding the cardiac rate regressors to model 4 ($\Delta R_{\text{adj},5-4}^2 = 1.0 \pm 0.7\%$ in Table 2). This additional variance is also very close in magnitude to that explained by the RVT regressors ($\Delta R_{\text{adj},5-3}^2 = 1.2 \pm 0.8\%$ in Table 2) and is of a similar order of magnitude to the additional variance explained by the RETROICOR regressors ($\Delta R_{\text{adj},5-4}^2 = 3.8 \pm 1.2\%$ in Table 2). This means that it is worth including the lagged cardiac rate regressors in a full model that includes several other physiological regressors (RETROICOR and RVT).

Including only lagged cardiac rate regressors with the 8 baseline regressors (models B and C, Table 4) explained almost as much variance as the RETROICOR and 8 baseline regressors (model 2, Table 2) (although, as discussed above and seen when comparing Figures 9 a and b, the spatial distribution of the noise explained by these two sets of regressors is different). Therefore, if only the cardiac waveforms or peak times were available, it would certainly be worth using the cardiac rate and baseline regressors alone to explain physiological noise.

The fact that 5 (lags 0 to 4 TR) out of 21 lagged cardiac rate regressors explained a majority of the additional variance (Table 4) is consistent with the observation of the strongest correlations within these time shifts (Figures 3 a, 4 a, 5 a-d and 7 a) and gives additional justification for their use as physiologically relevant regressors in the main 5-model nested regression analysis in Table 2. Using 21 lags did explain slightly more variance, suggesting that adding more lagged cardiac regressors to model 5 in the main regression analysis could explain a little more variance. However, the total number of regressors used should always be kept small relative to the total number of degrees of freedom (or the number of timepoints in the study), as emphasized by the slight decrease in ΔR_{adj}^2 when the simulated cardiac rate regressors are added in models 3 and 5 in Table 3.

The reproducibility of the results can be assessed by comparing the results from different scans of the same subject (Table 1 and Figures 5 a and b). The mean WM correlation coefficients at a lag of 2 TR (12 s) for subjects B and D were highly reproducible with the mean GM correlation coefficients varying slightly more across sessions. Despite this greater variation, subject B always had fairly high GM correlation coefficients while those of subject D were low in both sessions, showing that individuals gave consistent results. This is reinforced by the strong similarity of figures 5 a and 5 b which shows that the temporal behaviour as well as the magnitude of the correlations was consistent within single subjects.

It is not clear why some subjects showed stronger correlations than others (see Table 1 and Figure 5 c)). This could be related to inter-individual differences in physiology. Contrary to what might be expected, no positive correlation was found for these subjects between the

standard deviation of the cardiac rate and the mean correlation coefficient in the GM at a lag of 2 TR. In other words, larger variations in cardiac rate did not necessarily result in stronger correlations. The absence of strong correlations between the simulated cardiac rate timecourse and the MRI data confirms that the correlations with the real measured heart rates are significant and are not artifacts of the data processing and analysis.

The fact that each slice was acquired at a slightly different time during a 3 s period in each 6 s TR was not explicitly accounted for in this work. However, slice-to-slice variations in the cardiac rate would not affect the results since the cardiac rate was smoothed and resampled before the correlation and regression analyses and the correlations revealed occur between fluctuations at frequencies much lower than the frequency of any slice-to-slice variations.

Since fMRI is based on haemodynamic changes in the brain, involving both changes in blood volume and blood flow, it can be expected that changes in cardiac rate (which could affect both blood volume and flow to the brain) will affect the fMRI signal. It is, however, difficult to infer a simple, direct physiological mechanism by which changes in cardiac rate may be linked with the BOLD fMRI signal since there are so many physiological factors that interact and influence both the cardiac rate and the BOLD signal. For example, the heart rate variability spectrum is affected by many different interacting physiological factors (Cohen and Taylor, 2002) such as sleep stage (Otzenberger et al., 1998), respiration and respiration-related arterial pressure fluctuations, sympathetic and parasympathetic nervous activity and the renin-angiotensin system (Akselrod et al., 1981). Even higher frequency variations in the heart rate (such as those at the respiratory frequency) may be aliased into the low frequency range investigated here since the TR is relatively long (6 s). Any insight into the physiological mechanism linking cardiac rate variations and BOLD fMRI signal variations might also shed light on the origins of the temporal patterns of correlations identified in this study.

There are several results that suggest that the mechanism proposed to explain the correlations between the RVT and the fMRI signal might also be partially responsible for mediating the cardiac rate correlations with the fMRI signal. The first result is that there is some overlap between group maps of the correlation of the resting-state BOLD fMRI signal with the cardiac rate and the RVT respectively. The second is the similarity of the regions in which the RVT and cardiac rate regressors explain additional variance in the signal (Figures 9 d and e). The third is that the temporal behaviour of the two correlations agrees to some extent in that the average latency found (Birn et al., 2006b) for the maximum negative correlation between the RVT and the BOLD fMRI signal was 5.4 s, 8.8 ± 2.6 s for the global resting-state fMRI signal, or 9 s (Smith et al., 2006) and the delay found here for the maximum negative correlation between the cardiac rate and the fMRI signal was 6-12 s, and a positive correlation was found between the cardiac rate and the RVT timecourses with no delay (or a 6 s delay) of the cardiac rate.

Variations in arterial CO₂ due to changes in the depth or rate of breathing were proposed (Birn et al., 2006b) to mediate the RVT-MRI signal correlations since CO₂ is a potent vasodilator and can therefore increase cerebral blood flow and thereby the BOLD signal. As well as vasodilation, changing CO₂ levels also trigger chemoreflexes that change the depth and rate of subsequent breaths, resulting in low frequency fluctuations (< 0.04 Hz). The cardiac rate could also affect and be affected by arterial CO₂ changes, leading to variations in the BOLD signal.

In conclusion, our results demonstrate that across-beat variations in the cardiac rate correlate with low frequency fluctuations in resting-state BOLD fMRI data. The strongest correlations are negative and occur in GM at time shifts between 6 and 12 s. In all subjects, regressors consisting of measured cardiac rate timecourses shifted by delays of between 0 and 24 s were

useful in explaining substantial additional physiological noise variance in the BOLD signal when included in a model with established physiological regressors.

This study indicates that it can be beneficial to include shifted cardiac rate timecourses as nuisance variable regressors to reduce the physiological noise in future studies. Including such regressors might be particularly important for resting-state functional connectivity studies based on low frequency fluctuations in the brain MRI signal but is also likely to improve the statistical power of fMRI studies in general.

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Figure 1.

An illustration of the processing steps in the extraction of the cardiac rate from the TTL pulse timecourse. The initial estimate of the heart rate from the inverse of the TTL pulse intervals is shown schematically in a. Figure b shows the removal of spurious heart rate timepoints from the whole cardiac rate timecourse. The effect of smoothing the cardiac rate timecourse with the Gaussian kernel is shown over a section of the timecourse in c and the effect smoothing on the spectrum of cardiac rate variations is shown in d. Figure e shows (over a small section of the cardiac rate timecourse) the final resampling so that there is one timepoint for every MRI image volume or 6 s TR period. The cardiac rate timecourse shown in b-e is that measured for the subject that appears in Figures 3, 4, 6, 7 and 9.

Figure 2.

The mean Fourier transform of the smoothed and resampled cardiac rate timecourse is plotted (prior to polynomial detrending and filtering). The Fourier-transformed data were averaged over nine subjects (excluding repeat sessions) and the error bars, displayed at every fourth data point for clarity, indicate ($\pm$) the standard deviation over the nine subjects.

Figure 3.

T-maps of the correlation between the measured (a) or simulated (b) cardiac rate and resting-state fMRI signal timecourses in one slice of a single subject for lags -10 to +10 TR (± 1 minute). The t-values above the threshold are shown overlaid on the first raw EPI image. The t-maps and images have been masked to exclude areas outside the brain. There is a small area of correlation that appears outside the brain where the skull-stripping failed to remove subcutaneous tissue.

Figure 4.

A single-subject map of t-values of the correlation of the resting-state fMRI signal timecourse with the measured (a) or simulated (b) cardiac rate timecourse shifted by 2 TR. The map is overlaid on the first raw EPI image and both have been masked to exclude areas outside the brain. There is a small area of correlation that appears outside the brain where the skull-stripping failed to remove subcutaneous tissue.

Figure 5.

The mean t-values of correlation between signal timecourses in the gray matter (black) and white matter (red) and the measured cardiac rate shifted over a range of lag times. Data for two scanning sessions from the same subject are shown in a) and b). The mean t-value in the gray matter is shown for each subject in c) and averaged across all subjects (with error bars equal to the standard error of the mean) in d). The stars in d) indicate those average t-values that were found in a further t-test to be significantly different from zero (two-tailed, $p < 0.05$). The t-values of correlation with the simulated cardiac rate are shown in e) for the same scanning session as in b). For ease of comparison, the same scale is used in Figures 5 a, b, c and e.

Figure 6. The maximum (positive or negative) correlation coefficient in each voxel in the brain between delays of -10 and + 10 TR. The data are for the same subject as in Figures 3-4.

Figure 7.

Lag histograms showing the lags between ± 10 TR at which voxels in the brain have the largest correlation coefficients between the measured (a) or simulated (b) cardiac rate timecourse and the resting-state BOLD signal. Figure 7 a shows the same data as in Figure 6 for the same subject as in Figures 3-4.

Figure 8.

Maps of group t-statistics of the correlation between the measured cardiac rate and MRI signal timecourses. The top row shows the statistics for lags of 1 and 2 TR (6 and 12 s) combined (maximum t over the two lags) and the bottom row shows the statistics for lags of 5 and 6 TR (30 and 36 s) combined (maximum t over the two lags). These pairs of lags were chosen since they had the most significant correlations in the gray matter (see Figure 4d). The t-statistics above a threshold of 3.09 ($p < 0.001$) are shown overlaid on the group averaged EPI image (MNI space). The t-maps were masked to exclude areas outside the brain.

Figure 9.

Maps of the successive differences in R^2_{adj} (ΔR^2_{adj}) between the nested regression models are shown to illustrate the effect of adding in each set of regressors. The differences displayed are $\Delta R^2_{adj, 2-1}$ (a), $\Delta R^2_{adj, 3-2}$ (b), $\Delta R^2_{adj, 4-2}$ (c), $\Delta R^2_{adj, 5-4}$ (d), $\Delta R^2_{adj, 5-3}$ (e) and $\Delta R^2_{adj, 5-1}$ (f). The maps are scaled between 0 (black) and 0.1 (white) except for the final map in (f) which is scaled between 0 (black) and 0.2 (white). These results are for the same subject as shown in Figures 3, 4, 6 and 7.

The cardiac rate and the correlation coefficients between the cardiac rate and the resting-state fMRI signal in gray and white matter voxels at a lag of 2 TR. The heart rate statistics were collected from the smoothed and resampled cardiac rate timecourses prior to detrending and filtering. The asterisks indicate the sessions that were excluded from the group analysis.

Table 1

Subject	Heart Rate (Hz)		Correlation Coefficient at Lag = 2 TR (12 s)			
	Mean	Standard Deviation	GM Mean	GM SD	WM Mean	WM SD
A	1.04	0.066	-0.205	0.005	0.098	0.090
B	1.02	0.065	-0.270	-0.022	0.112	0.099
B*	1.05	0.061	-0.174	-0.038	0.090	0.076
B*	1.07	0.084	-0.121	-0.024	0.072	0.058
C	0.98	0.100	-0.090	-0.011	0.049	0.048
D	1.15	0.115	-0.021	-0.001	0.045	0.045
D*	1.16	0.098	-0.003	-0.005	0.044	0.049
E	1.10	0.076	-0.042	0.003	0.057	0.056
F	0.86	0.121	-0.027	0.005	0.078	0.090
G	0.83	0.060	-0.098	0.000	0.059	0.065
H*	1.16	0.073	-0.025	-0.013	0.052	0.050
I	0.95	0.072	0.001	-0.003	0.053	0.056
Mean over all sessions	1.03	0.083	-0.090	-0.009	0.068	0.065
SD over all sessions	0.11	0.02	0.09	0.01	0.02	0.02

The whole brain mean R^2_{adj} and ΔR^2_{adj} values, mean and SD over all 9 subjects (one scanning session included per subject), for five nested regression models with physiological regressors including five lagged measured cardiac rate timecourses.

Model	Regressors				Mean R^2_{adj} over whole brain		Model Comparison	Mean ΔR^2_{adj} over whole brain	
	8 Polynomials	8 RETROICOR	8 lagged RVT	5 lagged cardiac rate	Mean across subjects	SD across subjects		Mean across subjects	SD across subjects
1	X				0.400	0.102	2-1	0.038	0.012
2	X	X			0.438	0.099	3-2	0.015	0.010
3	X	X		X	0.452	0.093	4-2	0.016	0.013
4	X	X	X		0.454	0.091	5-4	0.010	0.007
5	X	X	X	X	0.464	0.088	5-3	0.012	0.008
							5-1	0.064	0.025

Table 3

Identical to Table 2 but including five lagged simulated cardiac rate timecourses as a control. The whole brain mean R^2_{adj} and ΔR^2_{adj} values, mean and SD over all 9 subjects (one scanning session included per subject) are given for five nested regression models.

Model	Regressors					Mean R^2_{adj} over whole brain		Model Comparison	Mean ΔR^2_{adj} over whole brain	
	8 Polynomials	8 RETROICOR	8 lagged RVT	5 lagged simulated cardiac rate		Mean across subjects	SD across subjects		Mean across subjects	SD across subjects
1	X					0.4000	0.1024	2-1	0.0375	0.0122
2	X	X				0.4375	0.0986	3-2	-0.0003	0.0008
3	X	X		X		0.4373	0.0988	4-2	0.0160	0.0126
4	X	X	X			0.4535	0.0911	5-4	-0.0001	0.0009
5	X	X	X	X		0.4534	0.0913	5-3	0.0162	0.0127
								5-1	0.0534	0.0203

Table 4

The whole brain mean R^2_{adj} and ΔR^2_{adj} values, mean and SD over all 9 subjects (one scanning session included per subject), for three nested regression models including only measured cardiac rate timecourses as regressors.

Model	Regressors	Mean R^2_{adj} over whole brain		Model Comparison	Mean ΔR^2_{adj} over whole brain	
		Mean across subjects	SD across subjects		Mean across subjects	SD across subjects
A	8 polynomial baseline	0.400	0.102	B-A	0.016	0.011
B	A + 5 lagged cardiac rate	0.416	0.097	C-A	0.024	0.015
C	A + 21 lagged cardiac rate	0.424	0.094	C-B	0.008	0.006