Characterization and reduction of cardiac- and respiratory-induced noise as a function of the sampling rate (TR) in fMRI

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A B S T R A C T

It has recently been shown that both high-frequency and low-frequency cardiac and respiratory noise sources exist throughout the entire brain and can cause significant signal changes in fMRI data. It is also known that the brainstem, basal forebrain and spinal cord areas are problematic for fMRI because of the magnitude of cardiac-induced pulsations at these locations. In this study, the physiological noise contributions in the lower brain areas (covering the brainstem and adjacent regions) are investigated and a novel method is presented for computing both low-frequency and high-frequency physiological regressors accurately for each subject. In particular, using a novel optimization algorithm that penalizes curvature (i.e. the second derivative) of the physiological hemodynamic response functions, the cardiac- and respiratory-related response functions are computed. The physiological noise variance is determined for each voxel and the frequency-aliasing property of the high-frequency cardiac waveform as a function of the repetition time (TR) is investigated. It is shown that for the brainstem and other brain areas associated with large pulsations of the cardiac rate, the temporal SNR associated with the low-frequency range of the BOLD response has maxima at subject-specific TRs. At these values, the high-frequency aliased cardiac rate can be eliminated by digital filtering without affecting the BOLD-related signal.

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Introduction

Cardiac induced pulsations are a common nuisance in fMRI data analysis and confound accurate detection of activation, especially in resting-state data where the temporal fluctuations of the signal associated with neuronal activation are weak (Bhattacharyya and Lowe, 2004; Biswal et al., 1996; Dagli et al., 1999; Hu et al., 1995; Le and Hu, 1996; Lowe et al., 1998). In the past, there have been many post-processing methods suggested to decrease the influence of cardiac noise in fMRI time-series analysis. These methods can be classified as retrospective correction techniques using external physiological recording of the cardiac pulse (Glover et al., 2000; Hu et al., 1995; Lund et al., 2006) or data-driven techniques (Beall and Lowe, 2007, 2010; Beckmann et al., 2005; Chuang and Chen, 2001; Greve and Dale, 2002; Perl barg et al., 2007). The former class of methods assumes that the temporal profile of the cardiac process at all voxels can be determined by a measurement of the cardiac pulse using a pulse-oximeter with sensor attached to one finger of the subject. More data-driven methods use Independent Component Analysis (ICA) to separate physiological noise sources from the data (Beckmann et al., 2005). It has been reported that spatial ICA can provide several components that are likely related to the cardiac cycle (Perl barg et al., 2007). In another study, it has been shown that temporal ICA may be better suited to extract cardiac-related components (Beall and Lowe, 2007). However, temporal ICA may be difficult to use for fMRI data due to the enormous size of the number of voxels present requiring a rather drastic reduction of the voxel space by PCA or other dimensionality reduction techniques.

Characterization of cardiac-related noise is complicated. The cerebral fMRI signal has been shown to vary considerably across the cardiac cycle due to sharp increases of blood pressure in the cerebral vasculature during the systolic phase causing an intracranial pressure wave (Dagli et al., 1999). The associated force leads to bulk motion of large brain regions such as the diencephalon and brainstem (Enzmann et al., 1992). Movement of CSF is also caused by the increase in cranial pressure, affecting ventricles and nearby regions (Piche et al., 2009). Furthermore, due to the high vascularization of the gray matter, global blood volume changes have also been reported at the capillary level during systole (Greitz, 1993). Thus, cardiac-induced noise at the capillary level may exist contributing to significant fluctuations of the BOLD response in fMRI. Since the blood pressure is a periodic function of time, the induced BOLD response will have major frequency components at the cardiac rate. However, it is known that the heart rate is not stationary across a typical time interval for fMRI scanning and shows small rate variations. These heart rate fluctuations can induce low-
frequency contributions (<0.1 Hz) affecting resting-state networks (Shmueli et al., 2007). In addition, it was observed that the cardiac rate and BOLD signal time courses in the resting-state were negatively correlated in the gray matter at time shifts of 6–12 s and positively correlated at time shifts of 30–42 s. Recently, this complex behavior of cardiac response function and BOLD signal was studied by estimating a cardiac-related hemodynamic response function consisting of the difference of a gamma and a Gaussian function (Chang et al., 2009). This response function is characterized by a peak at 4 s and a dip at 12 s. Modeling the cardiac-related BOLD response by a convolution of the cardiac-related hemodynamic response function and the cardiac rate could explain about 4% of the variance in resting-state gray matter voxels (Chang et al., 2009). The study by Chang et al. provides evidence that cardiac-induced BOLD signal contributions are more global and not only related to the vicinity of larger blood vessels.

A further component of the cardiac noise arises from the coupling of the respiratory and the cardiac cycle leading to major frequency contributions at the sum and difference of the fundamental cardiac frequency and respiratory frequency (Brooks et al., 2008). However, it has been reported that the coupling between cardiac and respiratory components in the gray matter is not very strong and, if present, only located to a small number of voxels (Beall, 2010).

The heart-rate during fMRI has been shown to be quasi-stationary during most studies (Shmueli et al., 2007). Standard deviations of the heart-rate were in general less than 0.1 Hz for the majority of their subjects. To reduce cardiac-induced noise, digital filtering has been used previously in rapid acquisition fMRI where the fundamental cardiac frequency did not alias (Biswal et al., 1996). In most fMRI studies, however, TR = 2 s is used leading to aliased frequency components of the cardiac rate which may overlap with task frequencies or low-frequency components of intrinsic neuronal networks (as in resting-state). To our knowledge it has never been studied if, after aliasing of the cardiac rate, band-pass filtering could be used to significantly reduce the effects attributed to the cardiac rate in fMRI. This raises the question, if certain sampling rates (TRs) of the EPI acquisition are more favorable than others to eliminate or at least reduce the effect of cardiac noise.

The goal of this study is to shed more light on solutions to the problem of physiological noise contamination in fMRI. In particular, we would like to answer the following questions: Which TRs are favorable and do not lead to aliasing of cardiac pulsations into the low-frequency BOLD range? How much of the physiological noise can be eliminated?

To answer these questions, we performed a detailed analysis of the physiological noise sources and computed the aliasing properties of cardiac noise and respiratory noise at different sampling rates.

**Methodology**

**Effect of aliasing**

Alias means “false identity”. In signal processing aliasing refers to the fact that high frequency components larger than the Nyquist frequency, \( f_{Nyq} \), are mapped into low frequency components (below the Nyquist frequency). Aliasing will always be present for any finite function \( f(t) \), because a finite function will contain an infinite frequency spectrum due to Fourier space properties. Thus, aliasing is always present in real data acquisition.

The relationship between the Nyquist frequency and the TR is given by

\[
\begin{align*}
    f_{Nyq} &= \frac{1}{2TR} \quad (1) \\
    &\text{According to signal processing (see Appendix A), the Fourier transform of a sampled function is obtained by} \\
    \hat{F}(\mu) &= \frac{1}{\Delta T} \sum_{n=-\infty}^{\infty} F(\mu - \frac{n}{\Delta T}) \quad (2)
\end{align*}
\]

where \( F(\mu) \) is the Fourier transform of the continuous function, \( f(t) \), which is then sampled by \( \Delta T \) (TR in fMRI), and \( \hat{F}(\mu) \) is the Fourier transform of the sampled function.

The cardiac frequency spectrum in the normal population during 5 minute resting intervals has a small standard deviation \( \sigma_f \) of the order of 0.06 Hz (Malik, 1996) and mean resting frequency typically in the range of 1 Hz to 1.3 Hz (http://en.wikipedia.org/wiki/Heart_rate). We approximate the cardiac frequency spectrum by a Gaussian distribution with a mean of \( \mu_f \) and standard deviation of \( \sigma_f \), yielding

\[
F_c(\mu) = \frac{1}{\sqrt{2\pi}\sigma_f^2} e^{-\frac{\left(\frac{\mu - \mu_f}{\sigma_f}\right)^2}{2}}.
\]

Using Eq. (2), we then obtain the distribution of the sampled frequencies by

\[
\hat{F}_c(\mu) = \frac{1}{\Delta T} \sum_{n=-\infty}^{\infty} \frac{1}{\sqrt{2\pi}\sigma_f^2} e^{-\frac{\left(\frac{\mu - \mu_f}{\sigma_f}\right)^2}{2}}.
\]

Since all frequencies will map to the interval \([-f_{Nyq}, f_{Nyq}]\), and positive frequencies are non-distinguishable from negative frequencies in the real world, we augment the positive frequencies with equivalent negative frequencies. Also, the zero frequency needs to be counted twice. This will give the following distribution:

\[
\hat{F}_c(\mu) = \frac{1}{\Delta T} \sum_{n=-\infty}^{\infty} \frac{1}{2\pi\sigma_f^2} e^{-\frac{\left(\frac{\mu - \mu_f}{\sigma_f}\right)^2}{2}} + e^{-\frac{\left(\frac{\mu + \mu_f}{\sigma_f}\right)^2}{2}} \quad (5)
\]

**Low frequency-contributions of the cardiac rate**

Cardiac fluctuations of the heart rate have been shown to cause more complicated changes in cerebral blood flow, indicating a signal low-pass filtering relationship between heart rate and the corresponding BOLD response (Shmueli et al., 2007). This relationship was determined recently using a deconvolution approach according to linear system theory. It was found that the cardiac-induced BOLD response can be described in general by a convolution of the low-frequency cardiac rate time series (obtained from physiological measurements) and a cardiac response function, \( h_c(t) \). In a recent publication, Chang et al. (2009) approximated \( h_c(t) \) by a difference of a gamma and a Gaussian function according to

\[
h_c(t) = a_1t^6e^{-\frac{t}{\tau_1}} - a_4e^{-\frac{(t-a_3)^2}{\tau_2}}.
\]

where \( a_1 = 0.6/1.0167, a_2 = 2.7, a_3 = 1.6, a_4 = 2.128/1.0167, \) \( a_5 = 18, \) and \( a_6 = 12 \) (Chang et al., 2009). The denominator in the expression for \( a_1 \) and \( a_4 \) arises from the normalization condition \( \text{var}(h_c(t)) = 1 \) that we impose in this research. Aliasing of \( h_c(t) \), however, will not occur at typical TRs used in fMRI because the frequency range of the low-frequency cardiac response function is less than 0.1 Hz.

**Frequency range of the neuronal BOLD response**

The BOLD response is characterized by the neuronal hemodynamic response function and can be written as a difference of two gamma functions, according to

\[
h(t) = \left( \frac{6}{16} \right) t^6 e^{-\frac{t}{\tau_1}} - c_1(t^6) - \left( \frac{16}{16} \right) e^{-\frac{t}{\tau_16}},
\]
The optimum parameters for the cardiac response function and respiratory response function are determined independently from each other because cardiac-affected voxels have very small overlap with respiratory-affected voxels.

Split up the data into two datasets where data1 is the data with TR=\{700,900,1100,...,2500\}ms and data2 is the data with TR=\{800,1000,1200,...,2600\}ms.

Choose data=data1

Select significant voxels at 0.05 for cardiac or respiratory activity, respectively, using the hemodynamic response functions according Eqs.(6,8) from previous research (Chang et al. (2009), Birn et al. (2008)).

For each voxel:
- Set up the design matrix by \( X = [X_1 X_2 X_4] \) for estimation of \( h_C(t) \) and \( X = [X_1 X_2 X_4] \) for estimation of \( h_R(t) \) where \( X_1(t) = C_{HF}(t + t_{OC}) \) and \( X_2(t) = R_{HF}(t + t_{OR}) \) are the high-frequency cardiac and respiratory waveform with optimum phase offset \( t_{OC} \) and \( t_{OR} \) at each voxel,
- \( X_3(t) = C_{LF}(t) \cdot h_C(t) \) and \( X_4(t) = R_{LF}(t) \cdot h_R(t) \) are the low-frequency cardiac and respiratory waveforms, respectively.

The hemodynamic response functions have the form

\[
h_C(t) = h_C^{(0)}(t) + \alpha \frac{d}{dt} h_C^{(0)}(t) \quad \text{where} \quad h_C^{(0)}(t) = a_1 t^{a_2} e^{-\frac{t}{a_3}} - a_4 e^{-\frac{t}{a_5}(t-a_6)^2}
\]

and

\[
h_R(t) = h_R^{(0)}(t) + \beta \frac{d}{dt} h_R^{(0)}(t) \quad \text{where} \quad h_R^{(0)}(t) = b_1 t^{b_2} e^{-\frac{t}{b_3}} - b_4 t^{b_5} e^{-\frac{t}{b_6}}.
\]

For a start estimate, we use the values of a’s and b’s according to Eqs.(6,8). Since \( a_1 \) and \( b_1 \) are arbitrary, we scale \( h_C^{(0)}(t) \) and \( h_R^{(0)}(t) \) so that \( a_1 = b_1 = 1 \).

Sample \( X \) at the corresponding TR, high-pass filter \( X \) and voxel time series to eliminate signal drift if necessary.

Calculate the squared residual error \( \eta \) by

\[
\eta = \varepsilon^T \varepsilon = (y-Xb)^T(y-Xb),
\]

where \( y \) is the voxel time series and \( b = X^+ y \) is the linear least squares solution of the general linear model.

For cardiac hrf

\[
\left\{ \begin{array}{l}
x_{\lambda,\mu}^{*} = \arg \min_{x} \left( \frac{\eta(x)}{\lambda} + \lambda \int_{0}^{30s} \left[ \frac{d^2 h_C(t)}{dt^2} \right] dt - \mu \right) \quad \text{for fixed } \lambda, \mu \quad \text{if data=data1}\\
\end{array} \right.
\]

or

\[
\left\{ \begin{array}{l}
y_{\lambda,\mu}^{*} = \arg \min_{y} \left( \frac{\eta(y)}{\lambda} + \lambda \int_{0}^{30s} \left[ \frac{d^2 h_R(t)}{dt^2} \right] dt - \mu \right) \quad \text{for fixed } \lambda, \mu \quad \text{if data=data1}\\
\end{array} \right.
\]

The optimal solution is obtained as \( x_{\lambda,\mu}^{*} = (a_1^{*}, a_2^{*}, a_3^{*}, a_4^{*}, a_5^{*}, a_6^{*}, \alpha^{*}) \) for the cardiac response function and \( y_{\lambda,\mu}^{*} = (b_1^{*}, b_2^{*}, b_3^{*}, b_4^{*}, b_5^{*}, b_6^{*}, \beta^{*}) \) for the respiratory response function.

Fig. 1. Flowchart of the algorithm to determine the cardiac and respiratory hemodynamic response functions.

where the units of \( t \) are in seconds, similar to Glover (1999). The corresponding frequency distribution is given by \( |\hat{R}(f)|/|\mu| \) and has a maximum at about \( \mu = 0.033 \) Hz and a range of approximately 0.1 Hz where the power spectrum has the value of 10% of the maximum at \( f = 0.1 \) Hz.

Thus, the induced frequency range of the BOLD response is approximately limited to the interval \( (0, 0.1) \) Hz (Cordes et al., 2001). Removing low-frequency drift less than 0.01 Hz of the fMRI signal time course will produce an effective frequency range of [0.01, 0.1] Hz of the BOLD response.
Typically, in the normal population the respiratory rate at rest during 7 minute intervals has a mean of the order of 0.2 Hz to 0.3 Hz (http://en.wikipedia.org/wiki/Respiratory_rate) and standard deviation \( \sigma_R \) (of the order of 0.07 Hz (G uit et al., 2007)). We approximate the respiratory frequency spectrum by a Gaussian distribution. The corresponding range of frequencies will not yield any major aliasing of the respiratory frequency spectrum by a Gaussian distribution. The corresponding range of frequencies will not yield any major aliasing of the respiratory frequency spectrum by a Gaussian distribution. The corresponding range of frequencies will not yield any major aliasing of the respiratory frequency spectrum by a Gaussian distribution. The corresponding range of frequencies will not yield any major aliasing of the respiratory frequency spectrum by a Gaussian distribution. The corresponding range of frequencies will not yield any major aliasing of the respiratory rate spectrum by a Gaussian distribution. The corresponding range of frequencies will not yield any major aliasing of the respiratory rate spectrum by a Gaussian distribution. The corresponding range of frequencies will not yield any major aliasing of the respiratory rate spectrum by a Gaussian distribution.

It is known that the change of the respiratory amplitude can induce low-frequency signal variations (less than 0.1 Hz) that can be described by a convolution of a function related to a change of the respiration volume per time, \( RVT(t) \) (Birn et al., 2008), with a respiratory-related response function parameterized by a two-gamma function \( h_{R}(t) \) of the form

\[
h_{R}(t) = b_1 t^{b_3} e^{-b_2 t^2} - b_4 t^{b_3} e^{-b_2 t^2},
\]

where \( b_1 = 0.6, b_2 = 2.1, b_3 = 1.6, b_4 = 0.0023, b_5 = 3.54, \) and \( b_6 = 4.25 \).

In a more recent publication, Chang et al. (2009) used a respiration variation function \( RV(t) \) instead of \( RVT(t) \), defined by

\[
RV(t) = \text{std}_R(R(t)),
\]

where \( R(t) \) is the respiratory waveform acquired by the respiratory belt with its standard deviation evaluated using a sliding window approach (window width \( w \)). In this study we use a slightly increased \( w = 10 \text{ s} \) for extra smoothness, whereas in Chang et al. \( w = 6 \text{ s} \) was used.

**Table 1**

Average frequencies and standard deviations for physiological noise sources.

<table>
<thead>
<tr>
<th>Subject</th>
<th>( C_{ph} ) (Hz)</th>
<th>( R_{ph} ) (Hz)</th>
<th>( C_{std} ) (Hz)</th>
<th>( R_{std} ) (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>1.01 ± 0.075</td>
<td>0.24 ± 0.056</td>
<td>0.052 ± 0.041</td>
<td>0.050 ± 0.045</td>
</tr>
<tr>
<td>#2</td>
<td>1.37 ± 0.073</td>
<td>0.21 ± 0.067</td>
<td>0.040 ± 0.035</td>
<td>0.048 ± 0.038</td>
</tr>
<tr>
<td>#3</td>
<td>0.77 ± 0.054</td>
<td>0.16 ± 0.043</td>
<td>0.061 ± 0.051</td>
<td>0.042 ± 0.040</td>
</tr>
<tr>
<td>#4</td>
<td>0.84 ± 0.069</td>
<td>0.18 ± 0.089</td>
<td>0.038 ± 0.038</td>
<td>0.025 ± 0.028</td>
</tr>
<tr>
<td>#5</td>
<td>0.82 ± 0.059</td>
<td>0.25 ± 0.032</td>
<td>0.050 ± 0.049</td>
<td>0.048 ± 0.040</td>
</tr>
<tr>
<td>#6</td>
<td>0.98 ± 0.067</td>
<td>0.19 ± 0.038</td>
<td>0.063 ± 0.050</td>
<td>0.064 ± 0.051</td>
</tr>
<tr>
<td>Mean</td>
<td>0.97 ± 0.220</td>
<td>0.21 ± 0.035</td>
<td>0.051 ± 0.010</td>
<td>0.046 ± 0.013</td>
</tr>
</tbody>
</table>

**Respiratory-induced frequencies**

Physiological noise and temporal SNR

Labeling the echoplanar signal as \( S \) and its standard deviation (over time) \( \sigma \), the temporal SNR, \( tSNR \), is given by

\[
tSNR = \frac{S}{\sigma} = \sqrt{\frac{\sum_{i=1}^{n} S^2}{\sigma_0^2 + \sigma_p^2}}
\]

where the signal independent noise (thermal noise) is written as \( \sigma_0 \) and the signal-dependent physiological noise is \( \sigma_p \). The temporal SNR is the important measure that directly predicts the success or failure of an fMRI experiment. Since the physiological noise increases with field strength (because it is proportional to \( S \)), it already becomes the major noise source at 3 T and ultimately limits the magnitude of the tSNR. Therefore, removing physiological noise by filtering or physiological modeling to increase the tSNR are promising techniques to improve detectability of activation in fMRI.

**Materials and methods**

**Subjects**

Subjects were 6 healthy undergraduate students with previous fMRI experience from the University of Colorado at Boulder: 1 female, 5 males, mean age 23 years old, and all right-handed. For fMRI, subjects were instructed to rest, keep eyes closed and be as motionless as possible.
Table 2
Parameters of cardiac response functions.

<table>
<thead>
<tr>
<th></th>
<th>$a_1$</th>
<th>$a_2$</th>
<th>$a_3$</th>
<th>$a_4$</th>
<th>$a_5$</th>
<th>$a_6$</th>
<th>$\alpha$</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>0.0984</td>
<td>2.02</td>
<td>2.81</td>
<td>0.0584</td>
<td>13.5</td>
<td>16.2</td>
<td>21.8</td>
</tr>
<tr>
<td></td>
<td>(0.641)</td>
<td>(2.20)</td>
<td>(1.88)</td>
<td>(0.682)</td>
<td>(33.2)</td>
<td>(14.3)</td>
<td>(3.59)</td>
</tr>
<tr>
<td>#2</td>
<td>0.00949</td>
<td>4.47</td>
<td>1.89</td>
<td>0.00917</td>
<td>14.8</td>
<td>12.7</td>
<td>73.4</td>
</tr>
<tr>
<td></td>
<td>(0.218)</td>
<td>(4.37)</td>
<td>(1.14)</td>
<td>(1.50)</td>
<td>(42.0)</td>
<td>(11.1)</td>
<td>(0.303)</td>
</tr>
<tr>
<td>#3</td>
<td>0.00121</td>
<td>4.91</td>
<td>1.53</td>
<td>0.00183</td>
<td>13.4</td>
<td>13.0</td>
<td>55.4</td>
</tr>
<tr>
<td></td>
<td>(0.253)</td>
<td>(4.47)</td>
<td>(1.07)</td>
<td>(1.99)</td>
<td>(22.7)</td>
<td>(9.82)</td>
<td>(0.241)</td>
</tr>
<tr>
<td>#4</td>
<td>0.00009</td>
<td>3.69</td>
<td>2.27</td>
<td>0.00115</td>
<td>17.7</td>
<td>11.4</td>
<td>66.3</td>
</tr>
<tr>
<td></td>
<td>(0.564)</td>
<td>(3.64)</td>
<td>(1.19)</td>
<td>(1.22)</td>
<td>(56.3)</td>
<td>(11.4)</td>
<td>(0.323)</td>
</tr>
<tr>
<td>#5</td>
<td>0.00037</td>
<td>4.34</td>
<td>1.94</td>
<td>0.00333</td>
<td>15.9</td>
<td>12.5</td>
<td>219</td>
</tr>
<tr>
<td></td>
<td>(0.256)</td>
<td>(4.27)</td>
<td>(1.14)</td>
<td>(1.51)</td>
<td>(44.0)</td>
<td>(11.2)</td>
<td>(0.304)</td>
</tr>
<tr>
<td>#6</td>
<td>0.00076</td>
<td>4.58</td>
<td>1.62</td>
<td>0.00876</td>
<td>14.5</td>
<td>12.8</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td>(0.362)</td>
<td>(4.11)</td>
<td>(1.12)</td>
<td>(2.04)</td>
<td>(23.6)</td>
<td>(9.69)</td>
<td>(0.252)</td>
</tr>
</tbody>
</table>

Fit of mean function (MSE = 6 × 10⁻³)

<p>| | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang et al.</td>
<td>0.6/1.0167</td>
<td>2.7</td>
<td>1.6</td>
<td>2.128/1.0167</td>
<td>18.0</td>
<td>12.0</td>
</tr>
<tr>
<td></td>
<td>0.06/0.5618</td>
<td>2.1</td>
<td>1.6</td>
<td>0.0023/0.5618</td>
<td>3.54</td>
<td>4.25</td>
</tr>
</tbody>
</table>

Note: The obtained cardiac response function was parameterized as $h_C(t) = h_C^{(0)}(t) + \eta_1 \beta e^{-\eta_2 (t)} + \eta_3 \beta e^{-\eta_4 (t)}$. The function $h_C(t)$ was scaled such that var($h_C(t)$) = 1.

Table 3
Parameters of respiratory response functions.

<table>
<thead>
<tr>
<th></th>
<th>$b_1$</th>
<th>$b_2$</th>
<th>$b_3$</th>
<th>$b_4$</th>
<th>$b_5$</th>
<th>$b_6$</th>
<th>$\beta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>12.9</td>
<td>2.25</td>
<td>0.628</td>
<td>0.0784</td>
<td>2.19</td>
<td>4.93</td>
<td>$-6.9 \times 10^{-5}$</td>
</tr>
<tr>
<td></td>
<td>(6.55)</td>
<td>(2.13)</td>
<td>(0.925)</td>
<td>(0.0358)</td>
<td>(2.30)</td>
<td>(4.69)</td>
<td>$1.4 \times 10^{-4}$</td>
</tr>
<tr>
<td>#3</td>
<td>0.682</td>
<td>2.12</td>
<td>1.56</td>
<td>0.00266</td>
<td>3.73</td>
<td>4.40</td>
<td>$8.9 \times 10^{-5}$</td>
</tr>
<tr>
<td></td>
<td>1.28</td>
<td>2.22</td>
<td>1.68</td>
<td>0.00496</td>
<td>3.23</td>
<td>4.22</td>
<td>$1.0 \times 10^{-4}$</td>
</tr>
<tr>
<td>#4</td>
<td>0.468</td>
<td>2.10</td>
<td>1.52</td>
<td>0.00184</td>
<td>3.87</td>
<td>4.51</td>
<td>$1.7 \times 10^{-4}$</td>
</tr>
<tr>
<td>#5</td>
<td>1.84</td>
<td>2.00</td>
<td>1.65</td>
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<td>3.03</td>
<td>4.38</td>
<td>$4.4 \times 10^{-4}$</td>
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<td>1.48</td>
<td>0.00035</td>
<td>3.50</td>
<td>4.38</td>
<td>0.0</td>
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</table>

Fit of mean function (MSE = 3.5 × 10⁻⁴)

<p>| | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Birn et al.</td>
<td>0.6/0.5618</td>
<td>2.1</td>
<td>1.6</td>
<td>0.0023/0.5618</td>
<td>3.54</td>
<td>4.25</td>
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</table>

Note: The obtained respiratory response function was parameterized as $h_R(t) = h_R^{(0)}(t) + \xi_1 \beta e^{-\xi_2 (t)} + \xi_3 \beta e^{-\xi_4 (t)}$. The function $h_R(t)$ was scaled such that var($h_R(t)$) = 1.

FMRI acquisition

FMRI was performed in a 3.0 T Trio Tim Siemens MRI scanner equipped with a 12-channel head coil and parallel imaging acquisition using EPI with imaging parameters: GRAPPA = 2, 32 reference lines, TE = 25 ms, FOV = 22 cm × 22 cm, 14 slices in oblique axial direction covering the prefrontal cortex, brainstem and cerebellum, thickness/gap = 3.0 mm/1.0 mm, resolution 64 × 64, BW = 2170 Hz/pixel (echo spacing = 0.55 ms), and 180 time frames. For each subject 20 time frames were acquired for each condition [(rest + condition), (condition + condition)]. The design matrix $X(t)$ = 1.

Physiological noise sources

The raw cardiac waveform, as measured by the pulse-oxygen, showed a non-stable signal amplification over time, presumably due to finger motion that changed the pressure of the finger tip on the pulse-oxygen or due to peripheral vasomotion. To normalize the amplitude of the cardiac waveform, the envelope function of the maxima of the cardiac peaks and the envelope function of the minima of the cardiac wave form were computed. The envelope functions of the minima and maxima were then interpolated at the measured time points of the cardiac rate. The amplitude of the raw cardiac waveform (distance of local maxima to minima) was then divided by the difference of the two envelope functions at each time point. This process normalized the cardiac amplitude to 1. The resulting wave form, called $C_R(t)$, represents the high-frequency waveform with average frequency in the 1 Hz range. The low-frequency cardiac waveform, $C_C(t)$, was determined by using a sliding window approach with a window width of $w = 10$ ms. To avoid artifacts at the edges of the window and to obtain a smoother frequency spectrum, $C_W(t)$ was multiplied with a Hanning filter (Welch, 1967). The frequency obtained from the sliding window approach was assigned to the midpoint of the window.

The raw respiratory waveform, as collected by the respiratory belt, was easier to process because the signal amplification did not change. No normalization of the signal was carried out and the high frequency respiratory wave function, $R_{HF}(t)$, was identical to the raw wave form. To determine the low-frequency respiratory waveform, $R_{LF}(t)$, we used the approach according to Chang et al. (2009), where the change of the standard deviation of $R_{HF}(t)$ was computed using a sliding window approach (the corresponding function is also called $RV(t)$). Also here, we chose a window width of $w = 10$ ms and used a Hanning filter. We also computed the RRF (according to Birn et al. 2008) and compared $R_{LF}(t)$ and RRF (t).

Data analysis

All fMRI data were corrected for differences in timing of slice acquisitions and realigned in SPM8 (http://www.filion.ucl.ac.uk/spm/). The design matrix $X$ was set up using the four regressors for the physiological noise sources. The first regressor $X_1(t) = C_{HF}(t + t_{LOC})$ is essentially the same as the high-frequency cardiac function $C_{HF}(t)$,
except that for each voxel time series, a temporal shift $t_0$ with $0 \leq t_0 \leq 1.2$ s was chosen such that the corresponding correlation coefficient is maximum with the voxel time course. To accurately determine $X_1(t)$, a cubic interpolation was used on $C_M(t)$ sampled at $\Delta T = 0.02$ s. This phase (i.e. time shift) optimization was done for each voxel so that possible delays of the high-frequency cardiac wave depending on the voxel location could be incorporated. Similarly, the second regressor $X_2(t) = R_H(t + t_{0R})$ is a time-shifted version ($0 \leq t_{0R} < 3$s) of the high-frequency respiratory function with maximum correlation coefficient to the voxel time course. The third regressor is the low-frequency cardiac waveform, given by $X_3(t) = C_L(t) \ast h_c(t)$. Similarly, the fourth regressor is the low-frequency respiratory waveform $X_4(t) = R_L(t) \ast h_d(t)$. All regressors were interpolated at the given $TR$ of the collected voxel time series. The design matrix $X = [X_1 X_2 X_3 X_4]$ and all voxel time series were then high-pass filtered using a cut-off frequency of $1/100$ Hz (Frackowiak, 2004) to eliminate low-frequency drift of the signal. All voxel time series and all regressors in the design matrix $X = [X_1 X_2 X_3 X_4]$ were variance normalized. A brain mask was used to effectively eliminate all non-brain voxels leading to an average of about 1300 voxels per slice. Standard smoothing using a Gaussian FWHM = 5 mm was carried out to increase the SNR.

**Subject-specific physiological response functions**

To determine subject-specific physiological response functions $h_c(t)$ and $h_d(t)$, we use an optimization technique with cross-validation, as outlined in Fig. 1. Since it is more accurate to determine $h_c(t)$ and $h_d(t)$ over such voxels that show significant activity of the corresponding waveforms, we determined both functions in separate runs using voxel time series for which each function is significant at the $p < 0.05$ level (uncorrected) using the functional forms of Eqs. (6) and (8) according to Chang et al. (2009) and Birm et al. (2008).

To determine optimized physiological response functions, first, we set up the voxel-specific design matrix $X = [X_1 X_2 X_3]$ (to determine the cardiac response function) or $X = [X_1 X_3]$ (to determine the respiratory response function). The matrix $X$ is sampled at the corresponding $TR$. The physiological regressors are formed by

$$X_1(t) = C_M(t + t_{0M})$$

$$X_2(t) = R_H(t + t_{0R})$$

$$X_3(t) = C_L(t) \ast h_c(t)$$

$$X_4(t) = R_L(t) \ast h_d(t)$$

where the time-shifts $t_{0M}$ and $t_{0R}$ were optimized for each voxel time series and the physiological hemodynamic response functions have the form

$$h_c(t) = h_c^{(0)}(t) + \alpha \frac{d}{dt} h_c^{(0)}(t)$$

and similarly

$$h_d(t) = h_d^{(0)}(t) + \beta \frac{d}{dt} h_d^{(0)}(t),$$

where

$$h_c^{(0)}(t) = a_1 t^{b_1} e^{-\frac{t}{\tau} - a_2 e^{-\frac{t}{\tau} - a_3} t}$$

and

$$h_d^{(0)}(t) = b_1 t^{b_3} e^{-\frac{t}{\tau} - b_4} - b_3 e^{-\frac{t}{\tau}}.$$
as the solution of the optimization problem for the cardiac response function.

Similarly, to determine the parameters for the respiratory response function, we solve for \( y = y_1 \) the optimization problem

\[
\{\hat{y}_{\lambda,\mu}\} = \arg \min_{y} \left( \frac{1}{n} \sum_{i=1}^{n} \left( \frac{d^2 h_i(t)}{dt^2} \right)^2 + \lambda \int_0^{30} \frac{d^2 h_i(t)}{dt^2} \right) \quad \text{for fixed } \lambda, \mu
\]

where \( \lambda, \mu \) are parameters that penalize the curvature of \( h_i(t) \). Then, for cross-validation we use \( y = y_2 \) and determine the optimized parameters by

\[
y_{\lambda,\mu}^* = \arg \min_{\{y_{\lambda,\mu}\}} \left( \frac{1}{n} \sum_{i=1}^{n} \left( \frac{d^2 h_i(t)}{dt^2} \right)^2 \right)
\]

Note that \( 0 < \frac{1}{n} \sum_{i=1}^{n} \left( \frac{d^2 h_i(t)}{dt^2} \right)^2 < 1 \). According to optimization theory (see for example Nocedal and Wright, 2006), penalty terms of the L1 norm-type are exact and it is only necessary to find one appropriate value of \( \lambda \) that is large enough where the solution of the equality constraint is satisfied for a given \( \mu \). In our case this value is \( \lambda = 1 \) for all \( \mu \in [1,30] \). The solutions to the optimization problems are obtained using the common Nelder–Mead algorithm, a derivative-free optimization method available in MATLAB (The MathWorks, Inc.).

Results

High- and low-frequency physiological waveforms

Table 1 lists the dominant frequencies of the physiological noise functions \( C_{HF}(t) \), \( R_{HF}(t) \), \( C_{LF}(t) \), and \( R_{LF}(t) \) for all subjects. The mean value of the high-frequency cardiac rate is 0.97 Hz but varies significantly among the subjects (range 0.84 Hz to 1.37 Hz). Similarly, the high-frequency respiratory rate is on average 0.21 Hz, but varies between 0.16 Hz and 0.25 Hz. The dominant frequencies of \( C_{HF}(t) \) and \( R_{HF}(t) \) are weakly correlated among the subjects (correlation coefficient = 0.23). The low-frequency cardiac rate has a mean value of 0.051 Hz and varies from 0.038 Hz to 0.063 Hz. Similarly, the low-frequency respiratory rate has a mean value of 0.046 Hz and varies between 0.025 Hz and 0.064 Hz. The correlation between the low-frequency cardiac waveform and the low-frequency respiratory waveform has a distribution, that, when pooled over all \( TR \) and subjects, is centered at zero with standard deviation equal to 0.18. Thus, there is no significant coupling between \( C_{HF}(t) \) and \( R_{HF}(t) \). Similarly, the correlation between the high-frequency waveforms \( C_{HF}(t) \) and \( R_{HF}(t) \) has a mean of zero with standard deviation 0.09. Also here, there is no significant coupling between \( C_{HF}(t) \) and \( R_{HF}(t) \).

Subject-specific physiological response functions

In Fig. 2, we show for the data from subject #1 the solution of the cardiac response function according to Eq. (18). We show explicitly how the functional form of \( h_C(t) \) changes for the average curvature \( \mu = \frac{1}{20} \int_0^{30} \frac{d^2 h_C(t)}{dt^2} dt = (2.7, 25) \). Tables 2 and 3 list the calculated parameters of the cardiac and respiratory response functions for all subjects, as determined by using the algorithm in Fig. 1. For the cardiac response function, the coefficient of the derivative term was significantly different from zero and needs to be explicitly included, whereas for the respiratory response function, the derivative term did not play any significance in reducing the error variance, and thus can be neglected. Note that the physiological response functions have been variance normalized. Table 2 also lists the approximations to the cardiac response function where the coefficient for \( \alpha \) is smaller (of order 1) such that the approximate cardiac response function
Note: Rows 1 to 3 list the estimated parameters \( \{a_1, a_2, a_3, a_4, a_5, a_6, \alpha\} \) of the cardiac response function for subject #1 from a single data set for estimation (see first column) and another single data set for validation (see second column). The last row contains the parameters for the full run using data1 and data2 (see Fig. 1, Table 2). The third column lists the optimum curvature \( \mu = \int_0^{|h(t)|} \frac{dt}{h(t)^2} \) where the minimum of the objective function occurred using the validation data set. The final column lists the mean-squared error (MSE) of each estimated cardiac response function to the optimized cardiac response function using all available fMRI data as listed for subject #1 in the last row and Table 2.

### Table 4

<table>
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<tr>
<th>Data set used for estimation</th>
<th>Data set used for validation</th>
<th>( \mu )</th>
<th>( a_1 )</th>
<th>( a_2 )</th>
<th>( a_3 )</th>
<th>( a_4 )</th>
<th>( a_5 )</th>
<th>( a_6 )</th>
<th>( \alpha )</th>
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<td>TR 700</td>
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<td>2.0061</td>
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<td>21.8294</td>
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</table>

The probabilities \( p(A < v) \) calculated by our method are shown in Fig. 8, to obtain a value of 10% or larger for the explained variance, we calculated for each subject the variance contribution of each physiological waveform \( \left( X_i \right) \) and all physiological waveforms \( \left( X_i X_2 X_3 \right) \) combined (see Table 6). Furthermore, we repeated the analysis using the previously published low-frequency physiological response functions of Chang et al. (2009) and Birn et al. (2008). As can be seen in Table 5, our approach yielded increased values of the explained variance (for example at \( p = 0.001, 18\% \) explained variance by our method versus 17.9\% explained variance using the previously published waveforms). To compare the above results with data that were not smoothed in the pre-processing stage, we repeated the analysis and computed the explained variance by all physiological regressors (Table 6). For all subjects, we obtained that the high-frequency regressors were able to explain more variance whereas the low-frequency regressors yielded a decrease of the explained variance. Overall, the combined effect of all 4 physiological regressors on using unsmoothed data was a reduction of explained variance for all subjects (compare Tables 5 and 6).

In Figs. 9(a-f) we show the locations of voxels that are affected by the high-frequency cardiac \( X_1 \) and respiratory \( X_2 \) waveforms, and the low-frequency cardiac \( X_3 \) and respiratory \( X_4 \) waveforms. It is very clear that \( X_1 \) (first row in Figs. 9(a-f)) affects mainly the brainstem region and the major blood vessels. Voxels in the prefrontal region are
not affected. The brain locations have a sparse appearance, and the number of voxels affected can vary significantly among all subjects. For example, subjects #2 and #5 show a very small number of voxels affected at the p < 0.01 level (yellow and white color). The influence of the high-frequency respiratory wave function (X4) can be quite strong for certain subjects (#1, #3, #5, #6) and shows many distinct locations throughout the brain, such as the prefrontal cortex, cerebellum, brainstem, temporal lobe, midbrain and occipital cortex (second row in Figs. 9(a–f)). Only for subjects #2 and #4 the affected regions are mostly cerebellum and visual cortex. Less cardiac activity does not imply less respiratory activity as subject #5 clearly shows. Here, the respiratory activity is very large compared to the cardiac activity. The voxels affected by the low-frequency cardiac waveform (third row in Figs. 9(a–f)) are concentrated at the region near the top portion of the cerebellum and the lower visual cortex as well as some focal regions in the medial prefrontal cortex. For all subjects except #6, the affected voxels show a sparse location. Subject #6, however, shows a large influence of low-frequency cardiac activity in visual cortex and prefrontal cortex. The low-frequency respiratory waveform (fourth row in Figs. 9(a–f)) has several regions in common with the low-frequency cardiac waveform (visual cortex, lingual cortex, temporal cortex, prefrontal cortex) (subjects #1, #2, #4, #6). For subjects #3 and #5, the low-frequency respiratory contributions are minor compared with the other subjects.

We also calculated highly significant clusters of physiological noise activity for a family-wise error rate FWE <0.05, as determined by AlphaSim in AFNI (Cox, 1996) using an individual p-value = 0.001 with cluster size of at least 24 mm³. For the high-frequency cardiac waveform, all significant clusters were at the brainstem and large blood vessels, and no cortical area was involved. For the high-frequency respiratory waveform, significant clusters were found in fusiform gyrus (subjects #1, #5, #6), lingual gyrus (subjects #1, #5) and cerebellum (subjects #1, #5, #6). The low-frequency cardiac waveform had significant clusters in caudate nucleus (subject #1), cerebellum (subjects #1, #2, #6), fusiform gyrus (subject #1), lingual gyrus (subjects #1, #2, #6), temporal cortex (subjects #1, #2, #6) and frontal cortex (subject #6). Significant clusters for the low-frequency respiratory waveform were found in calcarine cortex (subject #1), cerebellum (subjects #1, #6), lingual gyrus (subject #1), temporal cortex (subject #6) and frontal cortex (subject #6).

### Aliasing of high-frequency physiological waveforms as a function of TR

To show the effect of aliasing of the high-frequency cardiac rate, we parameterized the cardiac waveform of each subject by a Gaussian distribution with mean and standard deviation given in Table 1 and calculated the aliased frequency distribution after sampling by different TRs using Eq. (5). Fig. 10 shows the distribution of the high-frequency cardiac waveform of subject #6 and Fig. 11 the corresponding aliased frequency spectrum after sampling with TR = 2 s. Please note that Fig. 10 is a hypothetical cardiac waveform of subject #6, based on the Gaussian distribution and the mean and standard deviation values of subject 6. For better visibility of the effect of aliasing we have colored different frequency bands of the cardiac rate in Fig. 10 and show explicitly in Fig. 11 where each of the colored frequency bands aliases to. For example, the frequencies near 1 Hz of the peak region in Fig. 10 (red color) alias to the frequency-range larger than 0 Hz, whereas the frequency regions one standard deviation away from the peak in Fig. 10 (turquoise blue colors) alias to the frequency-range larger than 0.1 Hz.

Next, we calculated the probability that the distribution of the high-frequency cardiac waveform after sampling at a TR will be larger than 0.1 Hz. Fig. 12 shows the results of the probability p(f > 0.1 Hz) for all subjects and TRs from 0 to 4 s. As can be seen, there exist distinctive plateaus where p(f > 0.1 Hz) is maximum. For example, subject #6 with a cardiac rate of 0.98 Hz (σ = 0.067 Hz) has p(f > 0.1 Hz) ≈ 1 for TR < 0.8 s and 1.3 s < TR < 1.7 s. Also, in the vicinity of TR = 2.5 Hz the value for p(f > 0.1 Hz) has a maximum. In general, those TRs for which p(f > 0.1 Hz) is maximum (or close to maximum) offer advantages in terms of separating the cardiac influence on brain voxel time series associated with the high-frequency cardiac waveform from the low-frequency BOLD response, which is usually related to the frequency range f < 0.1 Hz because of the low-pass functional form of the hemodynamic response function. If this is the case, the cardiac noise that aliases to the f > 0.1 Hz range does not contaminate the BOLD frequency.
range and can be eliminated by digital low-pass filtering, providing voxel time-series with less variance from cardiac noise. Please note that the optimum TRs (when $p(f > 0.1\,\text{Hz}) \approx 1$) are different for each subject since the subjects had mean heart rates between 0.77 Hz and 1.37 Hz. However, each subject had a stable heart rate over a scanning time of 2 h with a small variance (compare Table 1). Thus, choosing a more optimal TR with less interference from cardiac noise is possible, especially if the study in question focuses on problematic areas that are known to vibrate with the cardiac rate, for example the brainstem.

As the TR can be optimal, it can also be detrimental to the data. For example, if a standard TR $= 2 \,\text{s}$ would have been chosen for subject 6, the value for $p(f > 0.1\,\text{Hz})$ is very low ($<0.2$), and all the high-frequency cardiac noise will alias into the $f < 0.1 \,\text{Hz}$ BOLD range.

For the high-frequency respiratory waveform, the aliasing behavior at typical TRs is very different (Fig. 13). Because of its lower mean frequency values (see Table 1), aliasing of the respiratory rate for $TR < 2.5 \,\text{s}$ will be very small leading to large values of $p(f > 0.1 \,\text{Hz})$ at typical TRs. Thus, there is no preference of certain TRs as long as TRs are chosen to be less than 2.5 s.

So far we considered only the high-frequency waveforms for the cardiac rate and the respiratory rate. The low-frequency waveforms for both physiological noise sources are less than 0.1 Hz and will not be affected by aliasing at typical TRs used in fMRI. Thus, in order to eliminate these low-frequency noise sources, digital low-pass filtering will not be possible. Only modeling will work, as we have shown here in the first part of this research.

Validation

So far we have assumed that the probability density function of the physiological noise sources is stationary for each subject during the entire fMRI scanning time of 2 h. This is a very strong assumption which needs validation. In the following we show that these assumptions are approximately true for the cardiac waveform using the collected pulse-oximeter data of all subjects by computing empirical results corresponding to the theoretical Figs. 10–12. In Fig. 14 (top) we show the cardiac frequency as a function of time for subject #6, as computed for one pulse-oximeter data set that was simultaneously recorded with the fMRI (TR 700 ms data) for this subject. Using kernel density estimation (Silvermann, 1986), we computed the probability density function of the cardiac frequency (Fig. 14 (middle)), which shows a maximum near 1 Hz and rapid fall-off for higher and lower frequencies. Using this empirically determined probability density function, we calculated the aliased frequency spectrum for a sampling rate $\Delta t = 2 \,\text{s}$ (using Eq. (2)) and determined the probability $p(f > 0.1 \,\text{Hz})$ by integrating all frequencies larger than 0.1 Hz (see Fig. 14 (bottom)). Next, to prove that the frequency probability density function is also quasi-stationary across the entire 2 h scanning time, we calculated the empirical mean probability $\overline{p}(f > 0.1 \,\text{Hz})$ and its standard deviation for all 20 pulse-oximeter data sets for each subject (which were collected over a 2 h time period while the subject was being scanned for fMRI), based on the frequency probability density functions that were estimated from all corresponding pulse-oximeter raw data. Results are shown in Fig. 15 for all subjects.

Temporal SNR

To compute the temporal SNR of our fMRI data, we have bandpass-filtered all raw fMRI data to remove low-frequency drift less than 0.01 Hz and removed all frequencies larger than 0.1 Hz to capture the dominant frequency region of the BOLD response. Fig. 16 shows the temporal SNR for all fMRI data (subjects #1 to #6) as a function of TR. Due to aliasing of the high-frequency cardiac rate, we get more or less aliasing into the low-frequency range ($f < 0.1 \,\text{Hz}$), resulting in smaller or higher temporal SNR, depending on the TR used. All subjects show an oscillatory behavior of the temporal SNR, similar to the curves in Fig. 12. From theory, there should be a high correlation of the probability that the cardiac waveform after sampling is above 0.1 Hz and the temporal SNR restricted to a frequency range less than 0.1 Hz. This is indeed the case for the majority of all subjects, as shown in Table 7. In fact, for subjects #1, #3, #4, and #6, the correlation coefficient between the equivalent curves in Figs. 12 and 16 is at least 0.24. For subject #3 the correlation coefficient is very high (0.65). Only for subjects #2 and #5, the correlation coefficient is lower ($-0.27$ for #2 and $-0.01$ for #5), which was expected because of the small number of voxels affected by the high-frequency cardiac waveform, as shown in Fig. 9e for subject #5 (top row). It is interesting to observe that the minima and maxima predicted by the aliasing analysis of the high-frequency cardiac noise (Fig. 12) indeed correspond well to the minima and maxima of the temporal SNR in Fig. 16.

Comparison with RETROICOR on temporal SNR

To determine the effectiveness of our method with an established method, we used RETROICOR (Glover et al., 2000). RETROICOR models the high-frequency physiological noise components by a low-order Fourier series that are expanded in terms of phases, which can be derived from external measurements. We used a Fourier series of order 2 for both cardiac and respiratory noise components, leading to 4 cardiac (2 sine functions, 2 cosine functions) and 4 respiratory regressors (2 sine functions, 2 cosine functions). After preprocessing with RETROICOR, we calculated the temporal SNR for voxels that have high-cardiac content. We also repeated the analysis using our proposed correction method for the high-frequency waveforms using $C_{\text{HR}}(t)$ and $R_{\text{HR}}(t)$ as regressors. Results are shown in Fig. 17. Here, the top graph shows that the temporal SNR is increased by about 10 units (on average) at specific TRs when RETROICOR is used in the preprocessing stage. For example, the temporal SNR of subject #1 is increased by about 15–18 units for the $TR$-interval [0.9 s; 1.2 s] when the high-frequency cardiac noise aliases into the $f < 0.1 \,\text{Hz}$ frequency range (see Fig. 15 top left). For other subjects, similar scenarios can be found. When our method is used, we obtain also an increase of 10 units (on average) of the temporal SNR. It is shown in Fig. 17 (middle graph), that RETROICOR and our method are comparable in eliminating cardiac noise contributions in fMRI data. However, small differences ($\Delta\text{SNR} < 4$) exist for several $TR$-intervals. For example, the temporal SNR of subject #3 is increased by about 0.27 for #2 and $-0.01$ for #5), which was expected because of the small number of voxels affected by the high-frequency cardiac waveform, as shown in Fig. 9e for subject #5 (top row). It is interesting to observe that the minima and maxima predicted by the aliasing analysis of the high-frequency cardiac noise (Fig. 12) indeed correspond well to the minima and maxima of the temporal SNR in Fig. 16.

For simplicity, in the previous comparison we have not taken into account the different numbers of regressors for our method and RETROICOR. From a statistical perspective, a simpler model is usually preferred over a more complex model (if all other parameters or features are equal). Thus, to assess the model fit of each method accurately and explicitly take into account the different numbers of regressors in the design matrix ($2$ for our method versus $8$ for RETROICOR), we computed for both methods the adjusted $R^2$ statistic (see for example Montgomery and Runger (2003)). In Fig. 17 (bottom graph) we show the difference in the adjusted $R^2$ statistic between our method and RETROICOR. This graph shows that the difference of the adjusted $R^2$ statistic is small and satisfies $0.06 \geq \Delta R_{\text{adj}}^2 > 0$ which implies that our method and RETROICOR have similar performance, since the average value $\Delta R_{\text{adj}}^2$ is about 0.03.

Discussion

The purpose of this research was to simultaneously estimate the physiological noise contributions arising from cardiac and respiratory activities in fMRI resting-state data by using physiological data acquired with pulse-oximeter and respiratory belt, and investigate the aliasing properties of the high-frequency cardiac noise as a
Fig. 9. (a), (b), (c). Subjects #1, #2, and #3. Locations of significant voxels associated with high-frequency cardiac activity (1. row), high-frequency respiratory activity (2. row), low-frequency cardiac activity (3. row), and low-frequency respiratory activity (4. row). The meaning of the color scale is: $p = 0.05$ (red), $p = 0.01$ (yellow), and $p = 0.001$ (white). The white dot visible in the structural images for the center slices is a vitamin D capsule (attached to the forehead) to indicate the right side.

(d), (e), (f). Subjects #4, #5, and #6. Locations of significant voxels associated with high-frequency cardiac activity (1. row), high-frequency respiratory activity (2. row), low-frequency cardiac activity (3. row), and low-frequency respiratory activity (4. row). The meaning of the color scale is: $p = 0.05$ (red), $p = 0.01$ (yellow), and $p = 0.001$ (white). The white dot visible in the structural images for the center slices is a vitamin D capsule (attached to the forehead) to indicate the right side.
function of TR. We have explicitly modeled the physiological noise by four different regressors. The first two regressors represented the high-frequency cardiac and respiratory activities. These functions were obtained from the physiological measurements and phase-optimized for each voxel to obtain the best time-shift of the regressors to accommodate the timing difference between the measured physiological waves at fingertip or abdomen and the different locations of cerebral tissue. Besides modeling of the high-frequency physiological noise sources, we have calculated the low-frequency changes of the cardiac and respiratory noise sources and computed a cardiac and a respiratory hemodynamic response function, optimized for each subject.

Optimization algorithm and cross-validation

A strength of this research is that the computed physiological hemodynamic response functions were not derived from specific voxels using a convolution approach but instead from an optimization algorithm with cross-validation using a parameterization of the cardiac and respiratory response functions with forms previously established (see Chang et al. (2009) and Birn et al. (2008)). We explicitly added a first-order derivative and applied constraints to allow for subject-specific variations of the hemodynamic response. With this subject-specific approach, low-frequency physiological response functions were obtained. We found that the off-diagonal elements of the covariance matrix of the four physiological regressors were not larger than 0.15 for variance normalized regressors, indicating a small overlap of the noise sources. Similar to the approach suggested by Chang et al. (2009), we used the standard deviation using a sliding time-window approach to determine the low-frequency respiratory waveform related to differences in the breathing inspiration rate instead of the approach used by Birn et al. (2008).

The methods proposed in this research are accurate, even if only a single fMRI resting-state data set is used for estimation and another fMRI resting-state data set is used for validation. We attribute the accuracy of the proposed method to the cross-validation step leading to accurate prediction of the physiological response functions, as shown explicitly for the cardiac response function of one subject (#1). Even if different data sets are used, the corresponding physiological response functions are similar.

The results obtained can also be slightly improved, if desired, by using both data sets for estimation and validation (i.e. using set1 for estimation, set2 for validation getting $h_c(t)$, then using set2 for estimation, set1 for validation getting $h_c(t)$), and then calculating the average of the obtained response functions (i.e. $\frac{h_c(t)+h_c(t)}{2}$). Switching estimation and validation steps will result in maximum efficiency to solve the optimization and validation problem.
maximum at about 4 s, a minimum at 10s and a second maximum at about 19 s, similar to our results. For all subjects we found that the inclusion of the derivative term in the model is necessary to determine the optimum cardiac response function. To obtain a subject optimized respiratory response function, we found that the solution of the optimization problem can be parameterized by the form given by Birn et al. (2008), but with different coefficients. There is no need for inclusion of a derivative term to obtain an optimum respiratory response function. Besides magnitude differences, we found that the occurrence of the undershoot is subject-specific and can occur between 4 s and 9 s. However, using subject-specific physiological response functions leads only to a small increase of the explained noise variance. In the study by Falahpour et al. (2013) there was small improvement in the average explained variance (similar to our results), but it was shown that using the subject-specific filters expands the explained variance in the entire brain.

We found that the difference in the respiratory response functions using the method by Chang et al. (2009) versus the method by Birn et al. (2008) is rather minor, since both functions are highly correlated with correlation coefficient larger than 0.7, according to our research.

Effect of spatial smoothing versus no smoothing

Spatial filtering is a common preprocessing technique that is used to increase the signal-to-noise ratio in fMRI data. Since high-frequency information is reduced by spatial filtering, it is conceivable that high-frequency physiological noise regressors will be less effective in smoothed data and may reduce the data correction. On the other hand, low-frequency effects caused by the low-frequency cardiac and respiratory hemodynamic response functions may show the opposite effects and lead to less data correction for unsmoothed data. Our analysis comparing the variance explained for smoothed versus unsmoothed data showed that by using all four noise regressors simultaneously, the data correction of all 6 subjects for smoothed data is still better than for unsmoothed data, due to a larger effect of the low-frequency physiological response functions on the data correction.

Appearance of activation maps

The subject-specific noise activity maps obtained have a sparse appearance and show that the physiological noise attributed to all four low- and high-frequency waveforms is more voxel-specific rather than affecting larger continuous regions of the brain. For example, the high-frequency cardiac waveform mostly affected the brainstem and larger blood vessels in the lower slices rather than the entire brain. Upper slices showed a very small amount of high-frequency cardiac noise, and it appears that most of the gray matter and brain periphery were not affected.

Existence of subject-specific optimal TRs

A particular focus of this research was to investigate if a subject-optimized TR can be chosen where the high-frequency cardiac rate does not alias into the low-frequency BOLD range. This is indeed the case as we have shown by computing the temporal SNR as a function of TR. Since the cardiac high-frequency activity was very stable for each subject during a 2 h of scanning time, it is possible to predict where the cardiac frequency will alias to. Even if the empirical probability density functions of the cardiac rate are computed from the pulse-oximeter data and the obtained density differs from an ideal Gaussian distribution, the variance of the density is still small enough so that aliasing after digital sampling is predictable and the empirical findings shown in Fig. 15 agree well with the theoretical predictions from Fig. 12. Thus, by knowing the mean cardiac frequency and its standard deviation of each subject (for example from pilot studies), it is possible to choose an optimal TR to reduce aliasing of the high-frequency cardiac noise into the low-frequency BOLD range. This approach could have

Nonparametric estimation of p-values

To arrive at accurate p-values of the explained variances by the physiological regressors, we used wavelet-resampling of the fMRI resting-state data to obtain approximate null data, and applied the same type of methodology that we used for modeling of the physiological noise sources to the null data. We found this step to be important to correct for the optimized time-shift selection at each voxel to obtain the high-frequency cardiac and noise regressors.

Comparison of the physiological response functions with other studies

The subject-specific physiological response functions obtained show some differences to the types proposed by Chang et al. (2009) and Birn et al. (2008). For example, with our approach we obtained cardiac response functions that have a first maximum between 1.5 s and 5 s and minimum between 11 s and 14 s. Furthermore, for one subject (#1) we obtained a pronounced second maximum at about 19 s which arises by the inclusion of the derivative term. A second maximum was also found by Chang et al. (2009) but not explicitly modeled. A more recent approach (Falahpour et al. (2013)) also showed a first maximum at about 4 s, a minimum at 10s and a second maximum at about 18 s, similar to our results. For all subjects we found that the inclusion of the derivative term in the model is necessary to determine the optimum cardiac response function. To obtain a subject optimized respiratory response function, we found that the solution of the optimization problem can be parameterized by the form given by Birn et al. (2008), but with different coefficients. There is no need for inclusion of a derivative term to obtain an optimum respiratory response function. Besides magnitude differences, we found that the occurrence of the undershoot is subject-specific and can occur between 4 s and 9 s. However, using subject-specific physiological response functions leads only to a small increase of the explained noise variance. In the study by Falahpour et al. (2013) there was small improvement in the average explained variance (similar to our results), but it was shown that using the subject-specific filters expands the explained variance in the entire brain.

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advantages for mapping activations of the brainstem or nearby spinal cord regions, which are inherently difficult to study with fMRI because of the large vibration associated with the heartbeat. As we have shown, the temporal SNR can be improved by about 40–50 in problem areas if an optimal TR is chosen. However, for the majority of the gray matter voxels in the upper cortex, high-frequency cardiac noise is relatively absent.

The results obtained in this research have been obtained for 2 h of resting-state data collection with 6 young healthy volunteers who had previous fMRI scanning experience. None of the subjects were recruited because of prior measurements of the heart rate. Furthermore, none of the subjects were selected based on a low variance of heart rate fluctuations. Thus, the subjects scanned were a true random sample of young students with prior fMRI experience. For activation data (instead of resting-state data), however, the method of finding an optimal TR may be less useful (depending on the task), because in activation data a larger variance of the heart rate fluctuations has been observed leading to less structured aliasing properties (Lund et al., 2006).

**Limitations of this study**

A limitation of this study is that only partial coverage of the brain was obtained, due to the short TRs used. Physiological noise affects have been shown in widespread regions of the brain (see for...
A computational limitation of this study is that the parameters of the cardiac and respiratory low-frequency hemodynamic response functions were determined independently. It is conceivable that a simultaneous estimation of both functions may have advantages and may be more accurate because other research have shown that there are extensive regions of the gray matter which are affected by both cardiac and respiration-related fluctuations (see for example Chang et al. (2009)). However, due to the large increase of local minima in the solution space going from 6 to 12 dimensions, finding a global constraint solution in a 12-dimensional space is considerably more challenging and beyond the aims of this research project.

Finally, we provided only a limited comparison with another established method (RETROICOR) to model the high-frequency cardiac and respiratory noise sources. Preliminary results indicate a similar performance between our method and RETROICOR, based on the increase of the temporal SNR and assessment of the model fit using the adjusted $R^2$ statistic. A more complete study of the differences, similarities and effectiveness of RETROICOR and our proposed method is beyond the scope of this research project.

Conclusions

In summary, modeling of all four physiological noise sources can lead to significant improvements in fMRI resting-state data quality. The high-frequency cardiac noise is mostly associated with the brainstem, nearby spinal cord and larger blood vessels. The cardiac noise affecting the brainstem and other nearby regions can be efficiently eliminated for fMRI using imaging at subject-specific TRs where the high-frequency cardiac noise will not alias into the BOLD frequency range.

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Appendix A

In the following, we derive the Fourier transform of a sampled continuous time-dependent function $f(t)$, as used in Eq. (2). Sampling $f(t)$ at discrete intervals $\Delta t$ yields the sampled function, $\tilde{f}(t)$, given by

$$\tilde{f}(t) = \sum_{n=-\infty}^{\infty} f(t-n \Delta T) = f(t) s(t)$$  \hspace{1cm} (A1)

where

$$s(t) = \sum_{n=-\infty}^{\infty} \delta(t-n \Delta T)$$  \hspace{1cm} (A2)

is the sampling function and

$$\delta(t) = \int_{-\infty}^{\infty} e^{-2\pi i \mu t} \, d\mu$$  \hspace{1cm} (A3)

is the Dirac delta function. Since the sampling function is periodic, it can be expanded in a Fourier series according to

$$s(t) = \sum_{n=-\infty}^{\infty} c_n e^{2\pi i n t / \Delta T}$$  \hspace{1cm} (A4)
where the Fourier coefficients, $c_n$, are calculated by

$$c_n = \frac{1}{\Delta T} \int_{-\infty}^{\infty} s(t) e^{-i2\pi n t/\Delta T} dt$$

$$= \frac{1}{\Delta T} \int_{-\infty}^{\infty} \sum_{m=0}^{\infty} \delta(t-m \Delta T) e^{-i2\pi n t/\Delta T} dt$$

$$= \frac{1}{\Delta T} \int_{-\infty}^{\infty} \delta(t-0) \Delta T e^{-i2\pi n t/\Delta T} dt$$

$$= \frac{1}{\Delta T} \delta(\mu-n\Delta T).$$

Thus,

$$S(t) = \frac{1}{\Delta T} \sum_{n=-\infty}^{\infty} \frac{c_n}{\sqrt{\pi}} e^{-\mu^2 / \Delta T^2}$$

(A5)

The Fourier transform of the sampling function, $S(\mu)$, where $\mu$ indicates the frequency variable, is obtained by using Eqs. (A2)–(A5). We obtain:

$$S(\mu) = \int_{-\infty}^{\infty} s(t) e^{-i2\pi \mu t} dt$$

$$= \frac{1}{\Delta T} \int_{-\infty}^{\infty} \sum_{m=0}^{\infty} \delta(t-m \Delta T) e^{-i2\pi \mu t} dt$$

$$= \frac{1}{\Delta T} \sum_{m=-\infty}^{\infty} \int_{-\infty}^{\infty} e^{-i2\pi (\mu-n\Delta T) t} dt$$

$$= \frac{1}{\Delta T} \sum_{n=-\infty}^{\infty} \delta(\mu-n\Delta T).$$

(A6)

Now, let $F(\mu)$ be the Fourier transform of $f(t)$. Furthermore, let the letter $\mathcal{F}$ indicate the Fourier transform operator and the symbol * to note convolution. Then, the Fourier transform of $f(t)$, $\mathcal{F} f(\mu)$, becomes using Eqs. (A1) and (A6):

$$\mathcal{F} f(\mu) = \mathcal{F} \{ f(t) (s(t)) \} (\mu) = \mathcal{F} \{ f(t) \} (\mu) * \mathcal{F} (s(t)) (\mu) = F(\mu) * S(\mu)$$

$$= \int_{-\infty}^{\infty} F(\mu) S(\mu) d\mu$$

$$= \frac{1}{\Delta T} \sum_{m=-\infty}^{\infty} \int_{-\infty}^{\infty} F(\mu) \delta(\mu-n\Delta T) d\mu$$

$$= \frac{1}{\Delta T} \sum_{m=-\infty}^{\infty} F(\mu-n\Delta T)$$

and the proof of Eq. (2) is complete.

References


