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Physiological denoising of BOLD fMRI data using Regressor Interpolation at Progressive Time Delays (RIPTiDe) processing of concurrent fMRI and near-infrared spectroscopy (NIRS)

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Abstract

Confounding noise in BOLD fMRI data arises primarily from fluctuations in blood flow and oxygenation due to cardiac and respiratory effects, spontaneous low frequency oscillations (LFO) in arterial pressure, and non-task related neural activity. Cardiac noise is particularly problematic, as the low sampling frequency of BOLD fMRI ensures that these effects are aliased in recorded data. Various methods have been proposed to estimate the noise signal through measurement and transformation of the cardiac and respiratory waveforms (e.g. RETROICOR and respiration volume per time (RVT)) and model-free estimation of noise variance through examination of spatial and temporal patterns.

We have previously demonstrated that by applying a voxel-specific time delay to concurrently acquired near infrared spectroscopy (NIRS) data, we can generate regressors that reflect systemic blood flow and oxygenation fluctuations effects. Here, we apply this method to the task of removing physiological noise from BOLD data. We compare the efficacy of noise removal using various sets of noise regressors generated from NIRS data, and also compare the noise removal to RETROICOR+RVT. We compare the results of resting state analyses using the original and noise filtered data, and we evaluate the bias for the different noise filtration methods by computing null distributions from the resting data and comparing them with the expected theoretical distributions.

Using the best set of processing choices, six NIRS-generated regressors with voxel-specific time delays explain a median of 10.5% of the variance throughout the brain, with the highest reductions being seen in gray matter. By comparison, the nine RETROICOR+RVT regressors together explain a median of 6.8% of the variance in the BOLD data. Detection of resting state networks was enhanced with NIRS denoising, and there were no appreciable differences in the bias of the different techniques. Physiological noise regressors generated using Regressor Interpolation at Progressive Time Delays (RIPTiDe) offer an effective method for efficiently removing hemodynamic noise from BOLD data.

Keywords

Physiological noise; Near-infrared spectroscopy; Functional magnetic resonance imaging; Correlation analysis; Resting state

Introduction

The primary sources of confounding noise in BOLD fMRI data are physiological fluctuations in blood flow and oxygenation due to cardiac and respiratory effects, spontaneous low frequency oscillations (LFO) in arterial pressure, or “Mayer waves” (Julien, 2006), and non-task related neural activity. While the hemodynamic variations arising from non-task related neural activity carry useful information about brain connectivity (Biswal et al., 1995; Damoiseaux et al., 2006; Fox et al., 2005; Greicius et al., 2003), in most cases, the purely physiological components only serve to obscure brain function by introducing substantial amounts of signal variance. Cardiac noise in particular is problematic, as the low sampling frequency of BOLD fMRI ensures that this signal is undersampled, and therefore strongly aliased in the recorded data. Various methods have been developed to estimate the noise signal through measurement and transformation of the externally measured cardiac and respiratory waveforms (e.g. RETROICOR and respiration volume per time (RVT) (Birn et al., 2008; Glover et al., 2000)), model-free estimation of noise variance through examination of residuals after task analysis (Madsen and Lund, 2006), or through spectral pattern classification of independent time series components (Georlette et al., 2007). The cardiac and respiratory waveforms used may be measured directly, or estimated from the BOLD data itself using temporal independent component analysis (ICA) (Beall and Lowe, 2007). However, these methods rely on a number of assumptions about how the physiological variations are manifested in the BOLD data.

We propose a different approach; exploiting a direct measurement of global flow and oxygenation fluctuation effects using NIRS. NIRS measures changes in concentration in oxy- ($\Delta[\text{HbO}]$) and deoxy-hemoglobin ($\Delta[\text{HbR}]$) at high temporal resolution (6–20 Hz), which allows unaliased sampling of respiratory and cardiac waveforms, which can be used to generate confound regressors.

Greve et al. (2009) have previously explored the use of NIRS for denoising BOLD data. However, we have found an important additional consideration for using this technique — accounting for the spatially dependent time lag between the NIRS and BOLD signal. The optimal time lag varies on a per voxel basis over a wide range. The values are both positive and negative, spanning up to 10 s; this likely accounts for the suboptimal performance of correlation with the undelayed signal in many locations. A preliminary analysis found that substantial reductions in confounding noise (and improved detection power) can be achieved by using multiple copies of the NIRS derived regressors over a range of delays as confound regressors (Frederick and Tong, 2010); however this is inefficient, as using large numbers of regressors unnecessarily reduces the degrees of freedom in the fitting process. We therefore set out to construct a parsimonious set of voxel specific regressors to efficiently fit and remove physiological confounds from BOLD data.

Materials and methods

Protocol

For this study, we reanalyzed concurrent fMRI/NIRS resting state data previously acquired for a different purpose (Tong and Frederick, 2011); the acquisition methods have previously been described in detail. In brief, a concurrent NIRS and fMRI study was conducted on 6 healthy volunteers (4 M, 2 F, aged 28.0 ± 4 years). Informed consent was obtained prior to scanning. The protocol was approved by the McLean Hospital Institutional Review Board. A 6 minute 30 second resting state MRI scan was performed on each subject while NIRS data were simultaneously recorded from a probe over the right frontal lobe. During the resting state scan, the participants were asked to lie quietly in the scanner while viewing a gray screen with a central fixation point.

fMRI acquisition and physiological monitoring

All MR data were acquired on a Siemens TIM Trio 3 T scanner (Siemens Medical Systems, Malvern, PA) using a 12-channel phased array head matrix coil. A high-resolution anatomic image set was acquired for slice positioning and coregistration of the functional data ((T1 weighted multiecho MP-RAGE3D (van der Kouwe et al., 2008)), resolution (RL, AP, SI) of $1.33 \times 1 \times 1$ mm, TI = 1100 ms, TR/TE1, TE2 = 2530/3.31, 11.61 ms, FOV = $171 \times 256 \times 256$ mm, $128 \times 256 \times 256$ pixels, 2 $\times$ GRAPPA, total imaging time 4 min 32 s). The resting state fMRI scan was acquired with the following parameters (Gradient echo EPI acquisitions with prospective motion correction (PACE), 2 dummy shots, 260 time points, TR/TE = 1500/30 ms, flip angle 75°, matrix = 64×64 on a 220×220 mm FOV, 29 3.5 mm slices with 0.5 mm gap parallel to the AC–PC line extending down from the top of the brain, GRAPPA acceleration factor of 3). Physiological waveforms (pulse oximetry, and respiratory depth) were recorded using the scanner's built-in wireless fingertip pulse oximeter and respiratory belt.

All MR data were preprocessed using the “First-level analysis->Pre-stats” option of FEAT, part of the FMRIB Software Library (FSL) (Smith et al., 2004; Woolrich et al., 2009) prior to further analysis — this consisted of motion correction, slice scan time correction, and spatial smoothing with a 5 mm Gaussian kernel (in that order). No temporal filtering was applied at this stage; all temporal filtering was applied during modeling.

NIRS acquisition

NIRS data were collected by means of an MRI compatible NIRS probe placed on each participant's forehead over the right prefrontal area (roughly between Fp1 and F7 in the 10–20 system (2007)) and held in place by an elastic band around the head. The probe (shown in Fig. 1) had two source and three detector optical fibers (with source-detector distances of 1 or 3 cm) embedded in a soft plastic sheet along with MRI-visible markers to identify the probe location on the anatomic MRI images. For this analysis, data was used from two collinear source detector paths sharing a source location, with spacings of 1 cm and 3 cm respectively. A near-infrared tissue imager (Imagent, ISS, Inc., Champaign, IL) was placed in the MRI control room and connected to the probe by 10 m long optical fibers. The sampling rate of NIRS data acquisition was 12.5 Hz, and two illumination wavelengths (690 and 830 nm) were used. NIRS data were recorded continuously during the MR exam.

Generation of BOLD denoising regressors

The RIPTiDe processing method for generating regressors for GLM analysis of BOLD timecourses from NIRS data has been described in detail previously (Tong and Frederick, 2010, 2011). Whereas before, we were interested primarily in exploring cerebral hemodynamics, in this study our goal is to model and remove the largest fraction of physiological variance possible from the BOLD data to facilitate further analysis. We therefore systematically altered various parameters in the generation of nuisance regressors using the NIRS data to determine their effects on the degree of noise removal and to optimize the noise removal procedure. We also calculated RETROICOR regressors from the physiological data recorded by the scanner, and compared the NIRS regressor method to RETROICOR.

NIRS waveform choice: $\Delta[\text{HbR}]$, $\Delta[\text{tHb}]$, or both

The two wavelength (690 and 830 nm) NIRS measurement we performed allows us to calculate two independent timecourses corresponding to the change in concentration of oxy- and deoxy-hemoglobin (denoted as $\Delta[\text{HbO}]$ and $\Delta[\text{HbR}]$ respectively) using the differential path length factor method (Matcher et al., 1994). By adding these two quantities, we can

also calculate the change in total hemoglobin concentration, $\Delta[\text{tHb}]$. Since we have two source measurements, only two of these quantities are independent. While any two of these three quantities carry all of the information in the NIRS measurements, $\Delta[\text{HbR}]$ and $\Delta[\text{tHb}]$ are particularly relevant to interpreting the changes in the BOLD signal. It has previously been established that changes in $\Delta[\text{tHb}]$ measured with NIRS correspond directly to changes in cerebral blood volume (Emir et al., 2008; Vernieri et al., 2004), and the ΔCBV ($\Delta[\text{tHb}]$) and $\Delta[\text{HbR}]$ waveforms appear explicitly in models of the BOLD effect (Buxton et al., 1998). Therefore we expect these two waveforms not only to model BOLD variance, but to model different physiological contributions to that variance, and to allow us to deduce the relative importance of these circulatory parameters in different regions.

NIRS source-detector distance

Source detector spacing has a strong influence on the effective depth of the NIRS tissue measurement. The average penetration depth of detected photons depends on several parameters, and in principle can be increased by increasing the source-detector distance at the expense of the signal-to-noise ratio (Del Bianco et al., 2002; McCormick et al., 1992). The NIRS probe used for this study, shown in Fig. 1, has 3 detectors and 2 source locations (each with a pair of illuminating fibers), giving 6 possible source-detector paths with various spacings; in order to determine the effect of sensor spacing on the quality of the denoising regressors, we generated regressors from the data both from B1 (10 mm) and C1 (30 mm), which lie along the same line and share a source location. The signal detected by the shorter source-detector path is believed to only come from extracerebral blood vessels, while the 30 mm source-detector spacing samples the cerebral cortex in addition to the extracerebral layer (McCormick et al., 1992; Saager and Berger, 2005). As a result, the short distance NIRS signals (B1) give a specific measurement of hemodynamic fluctuations from vessels, whereas the long distance (C1) NIRS timecourses reflect both this physiological variation and cerebral hemodynamic variations from additional sources (neural load alterations, etc.) (Gagnon et al., 2011). We hypothesize that the short distance signal, being more specific to purely physiological variation, will provide better noise removal from the BOLD data.

Single regressor versus multiple frequency band regressors

In our previous studies (Tong and Frederick, 2010, 2011), we used the raw or lowpassed NIRS timecourse, downsampled to the fMRI frequency to generate RIPTiDe regressors for GLM analysis. However, as noted by ourselves and others, there are distinct frequency bands in the NIRS data corresponding to separate physiological processes (very low frequency, low frequency oscillations, respiration, and cardiac effects), and the magnitude of the effect of each of these processes on the BOLD signal has a unique spatial distribution (Frederick and Tong, 2010; Greve et al., 2009; Thigpen et al., 2007). Since the relative effect size of the different frequency components of the different physiological sources varies across the brain, using a single timecourse to model all of the noise sources imposes a bias on the fit so that it matches BOLD data most closely in regions where the ratio of the contributions from the different physiological noise sources resembles that at the NIRS recording site. We hypothesize that splitting the NIRS timecourses into three regressors covering the low frequency (0.01–0.1 Hz), respiration (0.1–1.0 Hz), and cardiac (1.0–4.5 Hz) frequency bands prior to resampling will allow significantly better noise removal than using the raw NIRS regressor, decoupling the magnitude estimate of each frequency component, and removing this bias. To accomplish this, the NIRS timecourses were spectrally separated into 3 bands using a zero delay Fourier domain bandpass filter in Python. We have not found the very low frequency band (frequencies below 0.01 Hz) to be useful in these analyses (perhaps due to the dominance of instrumental noise in this region), so this band is omitted.

Common delay versus frequency specific delay

A further consideration affecting the fitting strategy is the observation that the different frequency components of the NIRS signal appear to propagate through the vasculature at different rates. As we reported previously, RIPTiDe regressors generated from the low frequency component of the NIRS signal show an orderly spatial progression of correlation with the BOLD data that suggests that the correlated signal is moving through the vasculature carried by bulk motion of the blood itself. This is consistent with NIRS regressors, especially $\Delta[\text{HbR}]$, reflecting endogenous fluctuations in blood oxygenation due to respiratory volume changes, which alter the ratio of oxy- to deoxy-hemoglobin in the blood entering the brain at any given time. It is also the case that the low frequency variations of blood pressure thought to account for Mayer waves will correspond to actual changes in the total amount of blood in any given voxel at a particular time, which will lead to propagating variations in $\Delta[\text{tHb}]$. Both of these effects depend on bulk blood motion from one place to another. The full span of delays expected for the low frequency signal is ~8–9 s, the time for full passage of all blood through the brain. This number comes from our previous observations over a number studies, and has been reported in radiotracer studies. For example, Crandell et al. (1973), show that in controls, blood from the carotids takes 2, 5.4, and 8.5 s to reach the anterior and middle cerebral arteries, gray matter in the cerebral hemispheres, and the superior sagittal sinus, respectively. In contrast cardiac pulsations appear to move through the vasculature much more quickly, as they are transient pressure waves that move faster than the blood carrying them, rapidly affecting the total hemoglobin in a voxel. Performing the RIPTiDe analysis on the cardiac component of the NIRS signal gives very different optimal time delay values than those derived from the low frequency component. This means that using the same time delay values for each component will necessarily lead to suboptimal fitting and noise removal for some components. Therefore we performed individual delay calculations for each frequency band in the NIRS signal, in order to optimally remove each component, and compared this to using the same delay value (estimated from the low frequency component) for each frequency band.

Signals in the respiratory band do not behave like the LFO or cardiac bands; they are best correlated with the BOLD noise at a constant time lag, which does not vary in space. This would seem to indicate that noise in this frequency band couples to the brain with a different mechanism, perhaps through space coupling effects of susceptibility changes in the lungs during breathing. In this case the NIRS data may not be the best model for the signal variation — something closer to the actual chest wall motion may be better in this frequency range.

Delay estimation

The RIPTiDe method for generating optimally delayed NIRS regressors has been previously described in detail (Tong and Frederick, 2010, 2011). Briefly, candidate NIRS-based regressors are time shifted over a range of positive and negative delay values, resampled to the fMRI TR, and used as regressors in multiple GLM analysis of the BOLD data. The time delay corresponding to the maximum significance is determined for each voxel in the BOLD dataset, and a set of optimally delayed voxel specific regressors is generated. The range and time step over which the delay is varied depend on the component of the NIRS signal being evaluated. The range of optimum lag times for raw NIRS and LFO signals within each subject is ~8–9 s, but the minimum and maximum values depend on NIRS sensor location; the peak response is broad, and a time step of 0.5 s is sufficient to uniquely determine the peak delay time. By performing the estimation over a range of ± 10 s, we ensure that we capture this peak for any NIRS sensor position in all subjects. The optimal delay response for cardiac signals, on the other hand, varies more quickly, and the autocorrelation of the cardiac signal is pseudoperiodic at the average cardiac frequency, so a timestep of 0.1 s or

shorter is needed to properly fit the peak delay time. This is illustrated for one voxel of a single subject in Fig. 2. As mentioned above, since the pressure wave moves much faster than bulk blood flow, the optimal cardiac delay is constrained to a much smaller range (1–2 s), so a smaller search range is required, however Fig. 2 shows the delay estimates on the same scale as the LFO signal to demonstrate the periodicity. To illustrate the range and distribution of optimal delay parameters across the brain and between regressor types, a full set of delay maps for the tHb regressors for a single subject is shown in Fig. 3.

One point that bears some discussion is the use of slice scan time correction in preprocessing. RIPTiDe properly estimates and compensates for time delays due either to hemodynamic delay or to slice acquisition delay. Therefore, slice scan time correction is not necessary for the technique to work, however when it is not used, the slice delays appear in the hemodynamic delay maps generated in the intermediate calculation steps. This leads to delay maps with a zebra stripe appearance in the slice direction (since we use interleaved acquisition) that make interpreting the spatial pattern of hemodynamic delays (which we find interesting in their own right) much less straightforward. We have therefore opted to apply slice time correction to the data prior to the RIPTiDe calculation.

Sample rate and aliasing

One factor that may initially seem problematic in resampling NIRS regressors to the fMRI TR is the substantially lower sample rate of the fMRI data. Typical TR values for fMRI data acquisition are 2–3 s, so any physiological variation higher than 0.16–0.25 Hz will be aliased in the recorded fMRI data. This includes the cardiac (and to some degree, respiration) frequencies. Consequently, downsampling the NIRS data to this temporal resolution will cause these waveforms to be aliased.

The sampling window for a typical echoplanar image is 30–50 ms long, so variations of 10 Hz or slower can be considered approximately constant over the time required to record a single slice; the cutoff frequency of the NIRS data is 6.25 Hz, which falls well within this range. Therefore a simple resampling operation of the NIRS data (with no antialiasing filter applied) to the fMRI frequency will alias the NIRS signal in the same manner that the BOLD sampling aliases the physiological variation of the MR signal. Since the time delay estimation step of the RIPTiDe procedure determines the optimal delay time for each voxel in the image, this ensures that the physiological data is appropriately aliased at every location — even the variation in slice sampling time is accounted for by this procedure. Therefore signal aliasing does not affect the ability of the NIRS waveform to fit the BOLD data, even for the cardiac waveforms.

RETROICOR+RVT regressors

We also calculated an expanded set of slice-specific RETROICOR regressors from the physiological data recorded from the built-in pulse oximeter and respiratory belt on the Trio scanner. Sine and cosine regressors for the cardiac and respiratory waveforms up to second order (8 regressors) were calculated using Glover's procedure, and the respiratory volume timecourse (RVT), convolved with the “Respiratory Response Function” (RRF) was calculated using the procedure detailed by Birn (Birn et al., 2008). We refer to these regressors as RETROICOR+RVT. We should note that due to the automatic gain compensation applied to the respiratory belt data prior to recording, the RVT that we calculated may not fully capture the lowest frequency variations in respiration. However, once the subject has settled down in the scanner, the respiratory waveform tends to be quite regular, and little (or no) rescaling is done over the course of the acquisition, so the respiratory waveform is still of some use. We did have to assume when calculating respiratory phase that the scaling was constant over the course of the acquisition, so that we

had the “global” maximum and minimum values. We note that many groups do use the physiological waveforms from the Siemens monitoring equipment to generate RETROICOR waveforms (for example, the PhLEM Toolbox does this), so this comparison, while not ideal perhaps, is not completely artificial.

GLM modeling for final regressor generation and denoising

Once a set of resampled denoising regressors was generated over a range of delay steps, each regressor was evaluated at each time delay using `film_gls`, the GLM calculation portion of FSL, and its associated utilities, to estimate the z-value of the correlation of the regressor with the preprocessed BOLD data at every voxel. Because the NIRS data reflects blood parameters directly, no hemodynamic response function was applied to the regressors. Prewhitening was applied in the estimation step. The z statistic maps were concatenated in time, and the peak z value across the lag time dimension was fit to determine the optimal delay time in each voxel. This time delay map was then used to generate the final, four-dimensional file containing the voxel specific delayed versions of each regressor. In the final step, the preprocessed BOLD data was then filtered by using a GLM filter implemented in Python to estimate and remove the contribution of each of the denoising regressors.

Performance evaluation

Evaluating the performance of the noise removal with NIRS consists of three equally important tests. The first test was to determine the total amount of variance that is removed from the signal by the various regressors, a quantity we seek to maximize, and choose the regressor sets that performed the best. However, this cannot be the only metric. The second test was to analyze the denoised resting state data to determine if the procedure actually improved the detection of resting state network activation (the purpose of performing the denoising operation). Third, we sought to confirm that the denoising procedure did not introduce excessive bias when compared with other denoising strategies which might limit the utility of the procedure in the analysis of task based fMRI data.

Noise removal efficiency

To compare the efficacy of noise removal using various regressor sets, we needed to select an objective metric of noise reduction. We used the voxel wise percentage of variance reduction as this metric. For each voxel in each subject, we calculate a spatial map of the variance over time, before and after using a GLM filter to fit and remove all the noise components in the set of regressors being tested. The percentage variance reduction (PVR) is defined as follows:

$$PVR = 100.0 \times \left(1.0 - \frac{\text{variance after GLM filtering}}{\text{original variance}} \right)$$

This provides a voxelwise measure of the amount of variance explained by the noise regressor set, which allows direct comparison of denoising strategies. The denoising procedure was performed for all combinations of the design choices described above for every subject. For each set of noise regressors, the 3D map of PVR was calculated for every subject. The individual subject maps were then transformed into MNI152 space and averaged, and the histogram of the PVR over all voxels in the average brain was calculated. The median PVR across the average brain using each regressor set was used as the figure of merit to compare analyses.

Resting state analysis test

For the analysis tests, data from 5 subjects were used (the data set for one subject was truncated and was not included in the analysis.) Three sets of data were compared in all analyses; the raw data with no noise removal, the data denoised with the “best” denoising NIRS regressor set selected using the above criterion, and the data denoised with the “best” RETROICOR+RVT regressor set. We performed an actual model-free analysis of the resting state data using probabilistic independent component analysis (Beckmann and Smith, 2004) to assess the performance of the different denoising strategies for a real analysis. FSL MELODIC was used to apply group PICA to each of the denoised datasets to compare the quality of the resting state network detection in each of the filtration conditions. In order to compare the results of the resting state analyses, the default mode network (DMN) was located in each analysis, and the relative strength of the network (relative to other components) and absolute strength (in terms of variance explained) were compared.

Task analysis with respect to simulated regressors

For the evaluation of task analyses, we followed a strategy similar to that implemented by Woolrich et al. (2001) in which we used the same three filtration conditions used in the resting state analysis to investigate the differences in the bias of the resulting statistical distributions by computing the z statistics at each voxel for four different dummy design paradigms. The z statistics form the empirical null distribution and an analysis technique with low bias will give a null distribution that closely approximates the theoretical Z distribution.

Four regressors were created to simulate the four dummy paradigms:

1. A boxcar design with a period of 60 s.
2. A single-event event-related (ER) design with a fixed inter-stimulus interval (ISI) of 15 s and a stimulus duration of 0.1 s.
3. A single-event jittered ER design with the ISIs drawn from a uniform distribution (minimum 13.5 s, maximum 16.5 s) and a stimulus duration of 0.1 s.
4. A single-event rapid ER design with randomized ISIs generated from a Gaussian distribution with mean = 6 s and standard deviation = 2 s, no ISI with less than 2 s and stimulus duration of 0.1 s. All four designs were convolved with the default gamma HRF used by FSL. The different denoised resting state datasets for each subject were analyzed with separate fixed-effect GLMs that included one of the four regressors above. The application of temporal high-pass filtering was also tested. Woolrich et al. investigated the impact of various methods to address the temporal autocorrelation in fMRI data, thus filtering for the paradigms was done in accordance with their recommendations and the recommended settings in FSL. Gaussian-weighted running-lines of fixed width are fitted and removed using a least-squares fit to remove trends no longer than the cutoff specified (Marchini and Ripley, 2000). Thus, the block design dummy paradigm was filtered with a cutoff of 60 s, the single-event ER design (#2) with fixed ISI was filtered with a 30 s cutoff, the other two ER designs were filtered by setting the full-width at half-maximum (FWHM) to 45 scans = 67.5 s.

Probability plots were created using the pooled set of z statistics from the analysis of all subject's data (for each specific analysis) to provide a better estimate of the tails of the empirical nulls, which is where inference takes place when multiple comparison corrections are taken into account (Woolrich et al., 2001).

Results and discussion

We successively applied the denoising procedure to the six subjects' data while varying the parameters used to generate the denoising regressors from the NIRS data. The amount of variance reduction achieved for each set of denoising regressors is shown in Table 1. One feature that simplified the analysis of the data was that the design parameter choices appear to affect the noise reduction performance in a simple, additive fashion — i.e. factors which improved denoising performance did so independent of any other design variations. This made it easy to optimize the noise reduction strategy, as there were no complex interactions between the design parameters. For comparison, a similar analysis for various combinations of RETROICOR and RVT physiological regressors is shown in Table 2.

Factors which affect denoising performance

Choice of NIRS species used—There has been some debate in the NIRS community regarding which species is most important in analyzing functional studies (HbR, HbO, tHb, or some combination), and how to interpret differing results in the different species. As mentioned in the Materials and methods section, we have two independently determined NIRS quantities — $\Delta[\text{HbR}]$ and $\Delta[\text{tHb}]$; each of the graphs in Fig. 4 shows, somewhat to our surprise, that for quantifying physiological variations in BOLD data, the $\Delta[\text{HbR}]$ and $\Delta[\text{tHb}]$ each explain a comparable fraction of the physiological variation in the BOLD data, and that they appear to be most effective in different areas, with $\Delta[\text{tHb}]$ regressors working most effectively near large vessels and in gray matter. The spatial distribution of the average degree of noise removal for each species is shown in Fig. 5. Since the amount of physiological variance explained is essentially additive, both species should be used; when regressors are generated from the spectrally separated, optimally delayed NIRS signals from the short distance NIRS probe, the amount of noise removed using both species (10.53%) is close to the sum of the amount removed by the HbR (5.90%) and tHb (6.76%) individually.

Spectral splitting of the NIRS signal and optimized delays—Comparison of the results obtained with and without splitting the NIRS regressors into spectral bands confirmed our suspicion that performing this spectral splitting, and applying separately optimized delays to each band, would allow significantly greater noise removal than leaving the regressor intact. This can be seen by looking down the columns of Fig. 4; for both the short (left column) and long distance (right column) source detector distances, going from using the unsplit regressors (first row), to split regressors (second row) to split regressors with optimized time delays (bottom row) progressively increases the total amount of variance removed by the NIRS regressors. In the case where both NIRS species measured at the short detector distance were employed, this condition removed 3.4 times as much variance as when the raw regressors were used. In this study, a single set of frequency limits was used to separate the spectral bands in all subjects; additional performance gains may be possible by setting the spectral band limits on a per-subject basis, based on their individual physiological data.

Source detector distance—Finally comparing the left column (short source detector distance) with the right column (long distance) in Fig. 4 shows that for every condition, the amount of noise removed by the more superficial measurement was higher than the amount removed using the probe that received cortical signals (10.53% vs. 8.89% in the case of split regressors). While at first it seems counterintuitive that the data from the NIRS probe that does not actually see the brain removes more physiological variance from the BOLD data in the brain than data from the one that does, this is consistent with the idea that the signal from the superficial probe is a more accurate representation of the purely physiological blood-borne signal we are attempting to remove. In fact, careful examination of the long distance

probe data shows that signal removal in brain directly below the probe and on the contralateral side is quite high (data not shown), which suggests that the signal recorded from this probe contains a significant amount of hemodynamic variation associated with the cortex. In this case, neural signals from the specific cortical region contaminate the NIRS signal, making it less effective for removing physiological noise. In contrast, the short distance probe data shows no such enhancement of the noise removal directly beneath the probe in any subject, leading us to conclude that any cortical contribution to the signal from that probe is not significant.

Comparison with RETROICOR+RVT—Fig. 6 shows the denoising performance of various combinations of RETROICOR and RVT regressors, and compares the best case noise removal with RETROICOR+RVT (cardiac and respiratory regressors to second order, and convolved RVT — 9 regressors total) to the best NIRS regressor choices (HbR and tHb waveforms used, data taken from the 1 cm source detector pair, NIRS waveforms split into three frequency bands (low frequency, respiratory band, and cardiac band), voxel specific delay time calculated for each regressor separately), 6 voxel specific regressors total shows that the NIRS regressors remove approximately 55% more variance than using RETROICOR+RVT. Fig. 7 compares the spatial distribution of the variance removal in these two cases. The improvement achieved with NIRS is particularly prominent in gray matter, where most activations of interest are presumed to be located.

There are four main factors which are likely responsible for the significantly larger fraction of BOLD noise explained by NIRS relative to RETROICOR+RVT. The first is that the NIRS regressors are a direct measurement of hemoglobin oxygenation and concentration, two factors that directly influence the BOLD signal. Using these measured quantities avoids any need to assume or derive the transformation from measured physiological waveforms (heartbeat and respiratory chest wall motion) to their effect on the BOLD signal. While the mappings developed for RETROICOR and RVT (low order Fourier expansion of the cardiac and respiratory phase waveforms and derivation of the respiratory depth function, respectively) do capture much of the timing information of variations in blood oxygenation and volume, the actual magnitude of these changes depends on the cardiac and respiratory phases in complex ways that are not modeled. Therefore, in general these waveforms will not be as close a fit to the hemodynamic parameters that account for the BOLD variation as the direct NIRS measurements.

The second factor that enhances noise removal with the NIRS regressors used here is the derivation of voxel specific, frequency specific timings for these regressors. We have seen that the optimal delay for fitting the noise signal varies over a wide range (as much 10 s from one part of the brain to another), and it is clear from Fig. 2 that even small errors in the lag time used will significantly decrease the quality of the fit, and hence the amount of noise removed. This is especially true for high frequency components such as the cardiac signal. Therefore the RIPTiDe delay estimation is critical to the noise removal performance for this method. Applying the RIPTiDe technique to optimize the delay of the RVT and RETROICOR regressors could provide a significant improvement in noise removal in the case where concurrent NIRS data is not available. Our preliminary investigation of this has shown a modest improvement to the median noise level removed with optimally delayed RETROICOR+RVT regressors, however this was not the focus of this study.

Third, the NIRS regressors account for HbR and tHb changes separately, as seen in the NIRS analysis, in any given voxel these may have different relative contributions to the BOLD noise. RETROICOR and RVT have no provision for modeling these effects separately.

Finally, aliasing effects on the cardiac and respiratory frequency hemodynamic waveforms are accurately accounted for in the RIPTiDe resampling procedure by estimating and applying the optimal delay time to the regressor at each voxel prior to resampling; this is only done indirectly in RETROICOR, which applies a constant delay compensation to each slice, relying on the relative intensity of the sine and cosine components of the model waveform to compensate for small time shifts. This will limit the amount of aliased noise that can be removed from the BOLD data.

To determine whether RETROICOR+RVT was removing any noise that was missed by the RIPTiDe method, we performed an analysis using both sets of regressors (data not shown). The results were not significantly different from using the best set of RIPTiDe regressors, leading us to conclude that the set of 9 RETROICOR+RVT regressors models a subset of the variance modeled by the 6 voxel specific RIPTiDe regressors.

Comparison with sham NIRS regressors—GLM filtering to remove physiological noise with arbitrary band-pass filtered low frequency noise signals can potentially result in variance reduction due to spurious correlations (as observed by Cooper et al. (2011)). To determine whether this was the source of our denoising performance, we repeated the best case NIRS filtering (HbR and tHb regressors from the short source-detector distance, split into bands, with optimal delays for each band — six voxel specific regressors total) using “sham” physiological regressors — each subject's fMRI data was filtered using NIRS data from a different subject. The median PVR throughout the brain was 6.4%, worse than all the analytical denoising strategies of similar order used, but somewhat close to the RETROICOR performance. This is consistent with the observations of Cooper et al.

Resting state analysis

The relative strength of the DMN compared to other components, and absolute strength (in terms of variance explained) for each denoising approach are shown in Table 3. These data show two things: 1) denoising using either RETROICOR+RVT or the NIRS regressor set increases both the relative and absolute strength of the DMN, and that of the two, the NIRS regressors result in a significantly larger improvement in detection, and 2) modeling and removing low frequency physiological noise removes structured noise (as evidenced by the reduction in the number of ICA components) without reducing the strength of the resting state networks; in contrast performing simple high pass filtering seems to remove signal power from the resting state networks, leading to a relative decrease in their strength.

Full exploration of the effect of physiological denoising on the strength of all the known resting state networks will require a larger dataset, which we are working to obtain.

Analysis with simulated regressors

The results of analysis with the dummy paradigm regressors are shown in Fig. 8. There was no observable deviation of either the RETROICOR+ RVT or RIPTiDe NIRS filtered data from the data with no physiological filtering, indicating that applying these filters would not increase the false positive rate of detection of these regressors. Because there was in fact no activation, this test was unable to assess whether the detection power increased, although it is not unreasonable to expect that this is the case, since the residual variance is decreased; as the previous test shows, detection of resting state networks is significantly enhanced.

Conclusions

NIRS provides a direct, robust measurement of the fluctuations in blood oxygenation and flow responsible for a large proportion of the variance in BOLD fMRI data. Despite the

local nature of the NIRS measurement, the NIRS waveform, especially in the low frequency (0.01–0.1 Hz), and cardiac (1.0–4.5 Hz) bands, contains information on global, rather than just local, physiological noise variation, by directly sampling systemic fluctuations in blood oxygenation and volume propagating through the cerebral vasculature. By using voxel specific delays, calculated separately for each of the frequency bands used, it is possible to account for the time it takes for blood and blood pressure variations to reach different parts of the brain, and to generate a small set of regressors that explain a large fraction of the physiological BOLD variance, and further, to remove this variance from the data. The $\Delta[\text{HbR}]$ and $\Delta[\text{tHb}]$ waveforms carry complementary information about physiological noise, and using both measurements significantly improves denoising efficacy. Furthermore, the physiological variations carried in blood are detected more specifically with a short source-detector distance (this source detector distance samples less cortical tissue than a longer distance probe, and is therefore biased to physiological rather than neural hemodynamic changes).

Recently, Cooper et al. (2011) performed an extensive study of NIRS denoising of BOLD data. Their study differs in focus and methodology (they focused primarily on combining the data from multiple NIRS probes, rather than spectrally separating and individually delaying the components of data from a single sensor), with the differences in the method for calculating PVR complicating a direct comparison of denoising performance between our approaches.¹ However, the main results are quite consistent. They too found that $\Delta[\text{HbR}]$ and $\Delta[\text{HbO}]$ (which is quite similar to $\Delta[\text{tHb}]$) each accounted for similar amounts of variance removal, in different regions; that optimized NIRS denoising was far more effective than RETROICOR; that sham regressors accounted for a surprisingly high amount of signal variance, comparable in magnitude to that removed by RETROICOR; and that using the optimal delay for a single probe regressor significantly improved denoising performance.

Correlational analysis of BOLD brain data has become a very active area of research in fMRI, and is being exploited to infer connectivity between brain regions even in the absence of a task. These efforts have primarily focused on the detection and quantitation of spatial patterns of simultaneous covariation in the BOLD data, largely because the low sampling rate of fMRI and the filtering caused by the hemodynamic response function make the effective determination of delays between regions on the timescale of neural transmission problematic. However, as we have demonstrated here and elsewhere (Tong and Frederick, 2010, 2011), at least for physiological variations, there are extremely significant correlations between the BOLD data in remote brain regions with relative delays of several seconds that can be exploited to provide information both about physiology and underlying neural activity. We believe that systematic study of the internal temporal coherence of BOLD fMRI data is a relatively unexplored area of research that is likely to yield other interesting results.

Concurrently acquired NIRS data explains a substantial fraction of BOLD noise, and using this data to remove physiological noise variance from BOLD data may allow more sensitive estimates of resting state and task related activations in fMRI data. Measuring blood oxygenation and volume fluctuations directly using NIRS avoids the need to calculate these effects from physiological waveforms that are indirectly related to the HbR and tHb fluctuations that affect the BOLD signal, and permits better noise removal than existing methods. Denoising using NIRS generated regressors performs very favorably relative to

¹Cooper's metric for PVR is the mean percentage variance removed from cortical gray matter, with a scaling factor for the number of degrees of freedom in the model; we used a simpler metric of median variance removed from the whole brain, without scaling by degrees of freedom, which will in general give lower PVR numbers.

RETROICOR+RVT, removing more than half again as much variance from the BOLD signal.

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Fig. 1. Schematic diagram of the optical probe. MR-visible markers are embedded in the probe to allow unique determination of the positions of the detectors and sources on the scalp from the anatomic MR images. The distances of source-detector pair B1 and C1 are 1 cm and 3 cm respectively.

Fig. 2.

Variation of the optimal delay time of the NIRS regressor in different spectral bands. The graphs show the z value of the fit of each regressor to the BOLD data in an occipital lobe voxel over a range of time lags ((a) shows the HbR derived regressors, (b) shows the tHb regressors — note that the z values are negated for the HbR fits). The z-statistic reaches a maximum at different time lags at different locations in the brain, and within different frequency ranges. These maxima are used to determine the optimal delay for each waveform in each voxel. Note that z value of the cardiac fit with delay is pseudoperiodic with lag value, due to the pseudoperiodic nature of the cardiac waveform.

Fig. 3.

Spatial maps of the optimal delay times for the various tHb regressors (LFO, respiratory, and cardiac) for a single subject. The LFO delays show the progression of blood from the arteries, through the parenchyma, to the draining veins, particularly the superior sagittal sinus, and cover a wide span (~8–9 s). The respiratory delays show very little spatial variation, suggesting the effects at the respiratory frequency are primarily through space coupling due to susceptibility variations due to chest wall motion. The cardiac delays cover a much smaller range than the LFO variations (approximately 2–3 s), and have a complex, but ordered spatial pattern.

Fig. 4.

Comparison of denoising performance of NIRS regressor sets. The histograms shown compare the percent reduction in signal variance achieved in every brain voxel by NIRS generated regressors. In each case the histograms are generated from an image of the average percentage of variance reduction over all six subjects registered to MNI152 space. Each individual graph compares the results of denoising using HbR only, tHb only, or both to generate regressors. (a) shows denoising performance for the short distance (1 cm) source detector pair, in the case where each species' raw timecourse is delayed and resampled to the fMRI TR, (b) shows results when the regressor is split into three spectral bands and delayed using the optimal delay for the low frequency component, and (c) shows results with

regressors split into three bands, using optimized delays for each frequency. (d), (e), and (f) show the same data in the same order for the 3 cm source detector distance.

Fig. 5.

Average percent variance removal maps, averaged over all 6 subjects for denoising regressors generated from the (a) $\Delta[\text{HbR}]$ and (b) $\Delta[\text{tHb}]$ waveforms. In both cases data is taken from the 1 cm source detector pair, the NIRS waveforms are split into three frequency bands (low frequency, respiratory band, and cardiac band), and voxel specific delay times are calculated for each regressor separately. Each fit uses 3 regressors total. The two figures use the same intensity scale (0% to 20% variance reduction). The $\Delta[\text{tHb}]$ regressors are particularly effective near blood vessels and in gray matter.

Fig. 6. Comparison of denoising performance for RETROICOR+RVT and NIRS generated regressors. (a) shows denoising performance for various combinations of the RETROICOR and RVT regressors. (b) compares denoising performance for RETROICOR+RVT with NIRS denoising using HbR and tHb, split into three spectral bands, with each band optimally delayed for both the 3 cm and 1 cm source detector distance.

Fig. 7.

Average percent variance removal maps, averaged over all 6 subjects for two choices of sets of denoising regressors. a) shows the best RETROICOR condition (cardiac and respiratory regressors to second order, and convolved RVT — 9 regressors total). b) shows the best NIRS regressor choices (HbR and tHb waveforms used, data taken from the 1 cm source detector pair, NIRS waveforms split into three frequency bands (low frequency, respiratory band, and cardiac band), voxel specific delay time calculated for each regressor separately) 6 regressors total. The same intensity scale (0% to 25% variance reduction) is used for a) and b). The NIRS variance removal is higher in most of the brain — the RETROICOR noise removal is superior only in the arteries at the base of the brain, near the Circle of Willis. The greater noise removal with NIRS is particularly prominent in the parenchyma.

Fig. 8.

Probability plots showing the pooled distribution of z values obtained in GLM analyses of 5 subjects versus various simulated regressors. The ideal distribution of z-values (Gaussian, mean 0, SD of 1) would fall along the dotted line in each plot; the markers indicate the observed z values. Deviation from the line in the clockwise direction about the center of the plot corresponds remaining inaccuracies in the modeling that are consistent with those observed by Woolrich et al. for the different dummy paradigms. The filtered conditions do not deviate significantly from the unfiltered data.

Median variance reduction over the whole brain (average of 6 subjects) for various sets of NIRS denoising regressors.

Table 1

Species	Raw waveform or band split	Delay type	Source-detector spacing	Total number of regressors	Median percent variance reduction
HbR only	Raw	Optimal for raw NIRS timecourse	3 cm	1	1.80
HbR only	3 bands	Single (computed from low frequency band)	3 cm	3	3.94
HbR only	3 bands	Optimal for each frequency band	3 cm	3	4.84
tHb only	Raw	Optimal for raw NIRS timecourse	3 cm	1	1.44
tHb only	3 bands	Single (computed from low frequency band)	3 cm	3	4.38
tHb only	3 bands	Optimal for each frequency band	3 cm	3	5.36
HbR, tHb	Raw	Optimal for raw NIRS timecourse	3 cm	2	3.09
HbR, tHb	3 bands	Single (computed from low frequency band)	3 cm	6	7.58
HbR, tHb	3 bands	Optimal for each frequency band	3 cm	6	8.89
HbR only	Raw	Optimal for raw NIRS timecourse	1 cm	1	1.67
HbR only	3 bands	Single (computed from low frequency band)	1 cm	3	3.77
HbR only	3 bands	Optimal for each frequency band	1 cm	3	5.90
tHb only	Raw	Optimal for raw NIRS timecourse	1 cm	1	1.40
tHb only	3 bands	Single (computed from low frequency band)	1 cm	3	4.40
tHb only	3 bands	Optimal for each frequency band	1 cm	3	6.76
HbR, tHb	Raw	Optimal for raw NIRS timecourse	1 cm	2	3.06
HbR, tHb	3 bands	Single (computed from low frequency band)	1 cm	6	7.59
HbR, tHb	3 bands	Optimal for each frequency band	1 cm	6	10.53

Table 2

Median variance reduction over the whole brain (average of 6 subjects) for various sets of RETROICOR +RVT denoising regressors.

Waveforms used	Total number of regressors	Median percent variance reduction
Respiratory RETROICOR waveforms (up to second order)	4	2.12
Cardiac RETROICOR waveforms (up to second order)	4	2.31
Convolved Respiration Volume per Time (RVT) waveform	1	1.95
Respiratory and Cardiac RETROICOR waveforms (up to second order)	8	4.63
Respiratory and Cardiac RETROICOR waveforms and convolved RVT	9	6.76

Table 3

Relative and absolute signal strength of the Default Mode Network (DMN) in an ICA analysis (components in each analysis are sorted in descending order of percent of variance explained).

GLM filtering	High pass filtering	Total ICA components detected	Component number of DMN	Percent of explained variance	Percent of total variance
None	100 s	37	26	2.28	0.99
RETROICOR+RVT	100 s	28	14	3.39	1.24
RIPTiDe NIRS	100 s	31	15	3.55	1.34
None	None	34	18	2.79	1.37
RETROICOR+RVT	None	30	2	5.90	2.66
RIPTiDe NIRS	None	30	1	6.68	2.85