

**INTRODUCTION**

Near Infrared Spectroscopy (NIRS) and BOLD fMRI measure complementary quantities relating to changes in the concentration of oxy- and deoxy-hemoglobin (HbO and HbR respectively) [1]. NIRS offers superior temporal resolution (40ms versus 2000ms), whereas BOLD offers superior spatial resolution and whole brain coverage. We are exploring the NIRS and BOLD relationship through simultaneous acquisition on human subjects along with measures of systemic physiology (respiration and cardiac). We have found that the NIRS time courses can account for approximately 25% of the resting-state BOLD fluctuations in cortex beyond that accounted for by the physiological measures alone. The spatial pattern of the NIRS-BOLD correlation was highly dependent on frequency band in which the NIRS was temporally filtered.

**Methods**

Five subjects underwent 3 resting-state and 3 task fMRI scans in a Siemens 3T scanner while two-wavelength (690 and 830nm) NIRS, respiration, and cardiac data (pulse oximeter) were simultaneously acquired. The scanner trigger pulse was also acquired in order to synchronize measurements.

**NIRS:** A bilateral NIRS probe with 8 sources and 16 detectors [2] was placed on the head, centered over the central sulcus (see Figure 8). The NIRS waveforms from 27 source/detector pairs were converted to HbR ("Deoxy") and HbO ("Oxy") concentration waveforms sampled at 25Hz. Approximately half of these channels were excluded from further analysis due to artifacts. The remaining waveforms were filtered into four bands at:

- 1) 0.05Hz (the "b-band"),
- 2) 0.10Hz (the "m-band" centered roughly on the Mayer wave frequency [3]),
- 3) 0.30Hz (the "r-band" centered roughly on the respiration frequency), and
- 4) 1.00Hz (the "p-band" centered roughly on the cardiac frequency).

This gave a set of about 13 waveforms each for each of the eight Hb-type/band combinations. Within each combination, the set of waveforms was reduced to 5 using a singular value decomposition (SVD). In addition, the 5 SVD waveforms for HbR and HbO were combined and reduced to 8 waveforms with another SVD. These SVD waveforms were then sampled at the time of the fMRI acquisitions and used as regressors in the analysis of the fMRI.

**Physiology/RETROICOR:** Cardiac waveforms were measured using a pulse oximeter (pulseox). Respiration waveforms were measured using either a pressure monitor under a belt or a stress gauge in series with a belt. Both were sampled at 25Hz. Regressors for the cardiac/pulse oximeter and respiration were created with RETROICOR Image CORection (RETROICOR) [4]. Each measure was modeled using a fundamental and harmonic for a total of four regressors each for cardiac and respiration. These regressor waveforms were then sampled at the time of the fMRI acquisitions and used as regressors in the analysis of the fMRI. Approximately half of the data sets were excluded because of some artifact in either the pulseox or respiration signals.

**Functional MRI:** each fMRI run was acquired with the parameter set used by the Functional Biomedical Informatics Research Network (fBIRN; www.nbirn.net), namely: EPI readout, TR=2000ms, flip angle =77°, TE=30ms, in-plane resolution of 3.43mm, slice thickness 4mm with 1mm skip, ascending slice order, echo spacing 0.5ms. Some fMRI runs were simple rest scans (5min), and some had a task (7.5min) in which 24 sec blocks of faces were presented interleaved with 12 sec of fixation. The fMRI were motion corrected (using AFNI 3dvolreg) and smoothed using a FWHM of 5mm.

**fMRI Analysis:** all fMRI analyses were performed using the FreeSurfer Functional Analysis Stream (FS-FAST, www.surferr.nmr.mgh.harvard.edu). Various linear models were constructed from the different regressors mentioned above or combinations thereof. When combinations were used, no attempt was made to orthogonalize the component except when HbR and HbO were combined (as mentioned above). In addition to the NIRS and physiological regressors, a third order polynomial was always included to account for linear trends in the fMRI. The regressor sets are coded as the following:

- ▶ T 3<sup>rd</sup> order polynomial, 3 regressors,
- ▶ P cardiac/pulse RETROICOR, 4 regressors
- ▶ R respiration RETROICOR, 4 regressors
- ▶ Dx HbR/Deoxy SVD for frequency band x, 5 regressors (Dx, Dm, Dr, Dp)
- ▶ Ox HbO/Oxy SVD for frequency band x, 5 regressors (Ox, Om, Or, Op)
- ▶ DxOx Combined Deoxy and Oxy regressors for band x, 8 regressors

The models are coded by combining the letters of their constituent parts (e.g., "PR" is the pulse and respiration RETROICORs combined with the polynomial, "Ob" is the b-band Oxy regressor set combined with the polynomial, etc). If the run had a task, it was modeled by convolving the task box car with a gamma function fMRI. The fMRI data were analyzed with each model (no temporal whitening was performed). In some cases, p-values were computed for certain regressor sets using an F-test (Figure 2).

The residual variance for model M ( $V_{qM}$ ) was computed at each voxel. To measure the performance a model, the variance reduction was computed relative to the variance of T-only as:

$$\text{Variance Reduction} = \text{VR} = 1 - V_{qM}/V_T$$

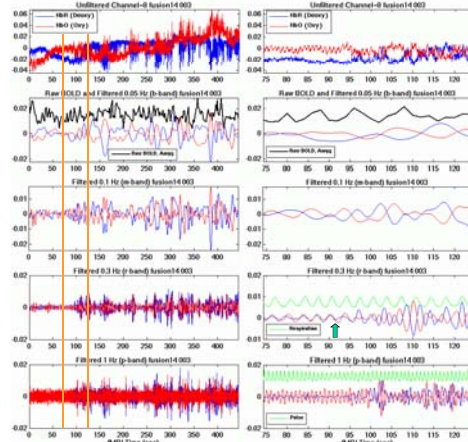
Larger VRs mean that the model removed more of the variance (eg, if VR=1, then model M removed all of the variance left unaccounted for by T by itself). Note that it is not necessarily the case that variance will decrease when more regressors are added. If the regressors do not model the underlying waveform better, then, in expectation, the residual variance will not change. The VR was computed both in the FreeSurfer common surface space and inside ROIs in order to facilitate comparison across subjects.

**Anatomical MRI:** an MP-RAGE (flip angle 7°, TR 2530ms, TI 1100ms, TE 3.44ms) anatomical volume was acquired for each subject and analyzed using FreeSurfer (www.surferr.nmr.mgh.harvard.edu) to generate subject-specific regions-of-interest (ROIs; Figure 7) as well as cortical surfaces registered to a surface-based common space (Figure 6). The anatomicals were aligned with the functionals using Boundary-based registration (BBR, [6]), which allowed the functional results to be mapped into the anatomical space for ROI and surface-based analyses.

**Results and Conclusions**

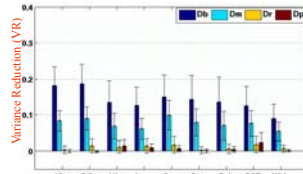
The results are shown in the figures to the right. From these results we draw the following conclusions:

- ▶ Deoxy and Oxy NIRS waveforms are highly correlated with fMRI BOLD waveforms (Figure 2) and able to reduce the BOLD variance by as much as 25% (Figures 4, 5, and 6).
- ▶ The correlations are spatially very widespread across the brain (Figures 2, 3, 4, 5, and 6) and extend far beyond where the NIRS optodes are located on the head (Figure 8).
- ▶ The strength of the correlations is highly dependent on frequency band, with lower frequencies (0.05 Hz) being the strongest (Figure 3).
- ▶ While Deoxy and Oxy waveforms tend to be highly anti-correlated (Figure 1) and contribute near equally to variance reduction (Figure 4), they still each contribute something that is unique (Figure 4).
- ▶ The low-frequency NIRS waveforms contribute something unique to variance reduction when compared to RETROICOR-based respiration and pulse in cortex (Figure 5), and together they combine to remove over 30% of the noise. It remains to be seen whether waveforms derived from systemic physiological measures (such as Respiration Volume per Time, or RVT [7]) can perform as well as NIRS.
- ▶ The r-band and p-band NIRS did not perform as well as the respiration and pulse RETROICOR (Figures 3 and 5), and it also remains to be seen whether another processing strategies would allow the NIRS measurements to account for the variance of systemic respiration and pulse measurements).



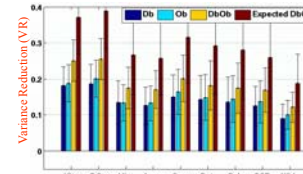
**Figure 1.** NIRS Oxy and Deoxy from a single source-detector channel, Amygdala BOLD, and physiology waveforms. The NIRS waveforms are shown unfiltered and band pass filtered at various frequencies. The left panel spans the entire fMRI acquisition; the right panel shows just that portion between the orange lines.

- The Oxy and Deoxy are, for the most part, closely anti-correlated, though the coherence will occasionally change sign (eg, r-band at t=90s marked with an arrow).
- The respiration-band and pulse-band filtered waveforms are clearly correlated with their respective physiological measures.



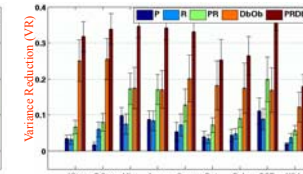
**Figure 3.** Effect of frequency band on Deoxy (HbR) NIRS fMRI variance reduction. This figure shows the VR averaged subjects for each of the 4 bands averaged over the given ROI (ROIs defined in Figure 7).

- Wide-spread variance reduction across all areas of the brain.
- The very low frequency (.05Hz) b-band is by far the most effective.
- Results for Oxy (HbO) (not shown) had a very similar pattern.
- The confidence intervals represent 1 standard error as measured across subjects.



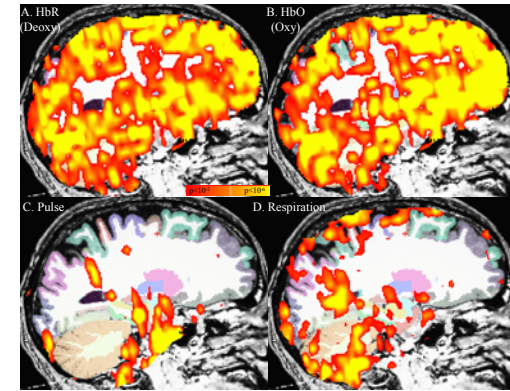
**Figure 4.** Effect of hemoglobin type on noise reduction, averaged across ROI (Figure 7) and subject.

- Expected DOb is the expected value of DOb in the case where Db and Ob are orthogonal.
- Deoxy and Oxy contribute about the same (cf Fig 2)
- Deoxy and Oxy are correlated but not completely with each providing something that is unique.
- The confidence intervals represent 1 standard error as measured across subjects.



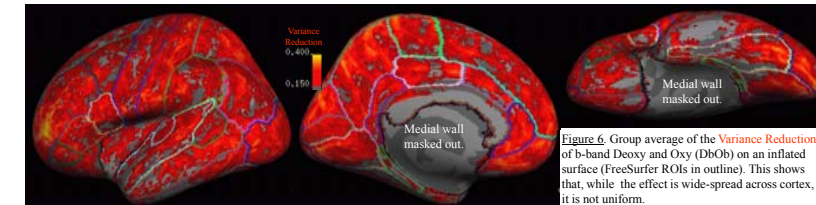
**Figure 5.** Comparison of systemic physiological measures with NIRS b-band (Deoxy and Oxy combined).

- Pulse and respiration account for about 7% in cortex
- Pulse and respiration account for much more in subcortical areas (about 15%).
- Respiration improves in outer cortex relative to inner.
- Combining all components together can give over 30% of variance reduction.
- The pulse and respiration contributions are:
  - Mostly independent of the Deoxy and Oxy b-band.
  - Better than the r- and p-bands (cf Figure 3)

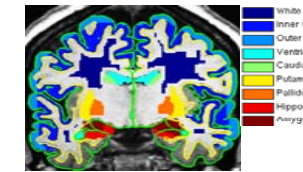


**Figure 2.** Significance maps of Deoxy (b-band), Oxy (b-band), Pulse RETROICOR, and Respiration RETROICOR regressors for an individual. Each component was analyzed in its own separate model.

- The Deoxy and Oxy activation:
  - Has a very wide spatial distribution.
  - Extends to areas much further away from where the probes are placed (cf Figure 8).
  - Is mostly in gray matter and CSF, less in white matter.
- Pulse correlations tend to be limited to brain stem and CSF.
- Respiration correlations are mostly limited to the edge of the brain and CSF.



**Figure 6.** Group average of the Variance Reduction of b-band Deoxy and Oxy (DOb) on an inflated surface (FreeSurfer ROIs in outline). This shows that, while the effect is wide-spread across cortex, it is not uniform.



**Figure 7.** FreeSurfer ROIs used in Figures 3, 4, and 5.

- ROIs are individualized
- Cortex excluded middle temporal and orbital frontal regions, medial wall, amygdala, hippocampus.
- Outer cortex: within 5mm of edge of brain
- Inner cortex: everything else
- White matter ROI excluded regions within 2mm of other tissue types.



**Figure 8.** Approximate placement of NIRS probes on the subject's right side (symmetrical probes on the left). The 4 optodes in the center strip are sources, the 8 optodes in the side strips are detectors. Each source emits two wavelengths. The NIRS waveforms are derived from 27 source-detector combinations.

**References:**  
[1] Huppert, et al, Neuroimage, 2006, p368. [2] Franceschini, et al, Psychophysiology, 2003, p548. [3] Julien, Cardiovascular Research, 2006, p12. [4] Glover, et al, MRM, 2000, p162. [5] Obata, Neuroimage 21:144 (2004). [6] Greve and Fischl, submitted. [7] Birn, et al, Neuroimage, 2006, p1536.

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