Analysis of Temporal Co-variations in the Hemodynamic Response to Neuroactivation Yields Additional Functional Information

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ABSTRACT

The study of event-related neuroactivation is a rapidly growing application area for functional near infrared spectroscopic imaging. One of the recognized advantages of fNIRS over BOLD-fMRI is that the former yields independent estimates of the position- and time-dependent concentrations of both oxygenated and deoxygenated hemoglobin. However, the algorithms used to analyze fNRIS data mostly have been direct analogues of methods developed by the fMRI community, with each component of the hemoglobin signal considered in isolation.

Recently we hypothesized (Wylie *et al*., *Neuroimage*, May 2009), that physiological information that is not readily accessible from single-component analyses resides in the manner in which the three components co-vary at a given location. We have explored this possibility by devising a six-valued combinatorial index of the interactions among the components, based on an appreciation of the manner in which blood supply normally responds to changing oxygen demand. Computation of the index involves noting whether the instantaneous hemoglobin concentrations are greater or less than their respective baseline mean values.

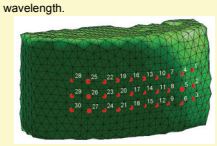
Here we report on the information content derivable from the combinatorial and single-component approaches, based on an **event-related activation study** (visual stimulus, *N* = 9) and on a **resting-state study** (*N* = 6) whose data was graciously supplied by Jan Mehnert of the Charité Univeristy in Berlin.

I. Visual Stimulus Study

Visual stimulus

Reversing checkerboard stimulus with 2 sec fixation, radius = 60 mm, visual angle = 9.5°, reversal rate = 8 Hz. Random inter-trial interval ensued from 11 to 20 seconds; one second intervals. Subjects were asked to maintain fixation throughout. 120 trials were presented. Age 22-36, mean = 27.6. 7-M, 2F.

Sensing Array Geometry: 30 Source x 30 Detector, dual wavelength.



Instrumentation: DYNOT 264 fNIRS tomography system (NIRx Medical Technologies, Glen Head, NY). Image framing rate ~ 2 Hz.

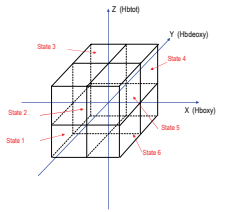
Data Analysis: 3D image recovery accomplished using Normalized difference method of Pei et al. (*Applied Optics*, Vol. 40, pp. 5755-5769 (2001). Best fit gamma variate function computed using AFNI. Random effects analysis conducted to detect voxel significance threshold across individuals. Corrections for multiple comparisons made by imposing cluster level and voxel level thresholds.

Computed Metrics: Time Fraction Analysis: Average time each voxel spends in selected Hb State in 20 sec period following presentation of stimulus. Null hypothesis: equal duration of time spent in Hb States 1 and 4, 2 and 5, and 3 and 6 under baseline conditions.

Volume Fraction Analysis: Partial volume occupied by each Hb state in selected Region of Interest (ROI). Null hypothesis: equal number of voxels in Hb States 1 and 4, 2 and 5, and 3 and 6.

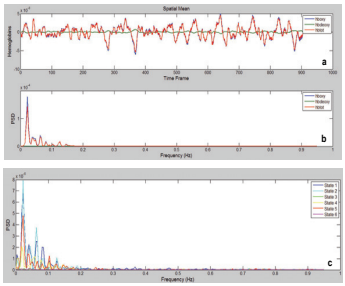
Resting State Study

Hb State Space and Magnitude of State Vector

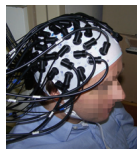


$$S = \sqrt{X^2 + Y^2 + Z^2} = \sqrt{(\mathrm{Hb_{oxy}})^2 + (\mathrm{Hb_{deoxy}})^2 + (\mathrm{Hb_{tot}})^2}$$

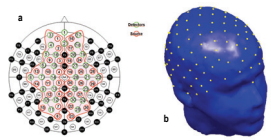
Hb Spatial Mean and Power Spectral Density



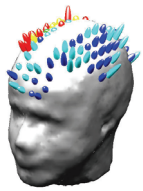
Data Collection



Source/Detector Configuration and 10-20 System

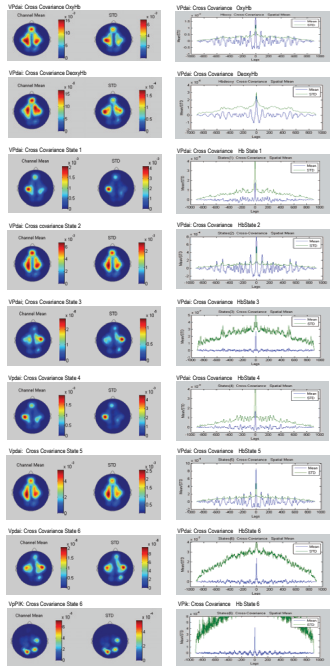


Hb State Vector Visualization Using Superquadratic Glyphs



Cross-Covariance of Hb Components and States: Channel Mean

(A) Spatial Map (B) Lag dependence

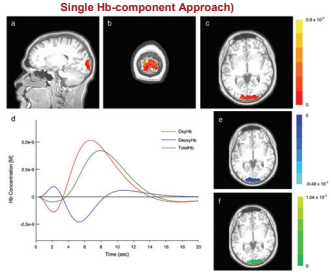


Visual Stimulus Study

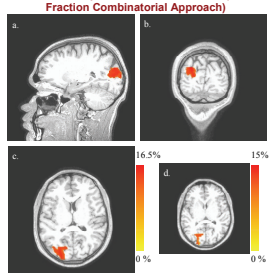
Definitions of Combinatorial States

Hemoglobin State	State 1	State 2	State 3	State 4	State 5	State 6
Hb_{oxy}	-	-	-	+	+	+
Hb_{deoxy}	-	+	+	+	-	-
Hb_{tot}	-	-	+	+	+	-
	Balanced	Uncomp. oxygen debt	Comp. oxygen debt	Balanced	Uncomp. oxygen excess	Comp. oxygen excess

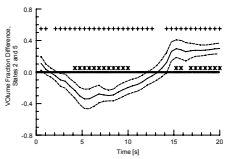
Activation Response to Visual Stimulus (Conventional Single Hb-component Approach)



Activation Response to Visual Stimulus (Time-Fraction Combinatorial Approach)



States 2 vs. 5 Volume Fraction Analysis



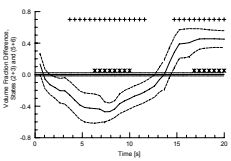
Statistical Significance of Single Hb-component Analysis

Hb Component	Number of Voxels / Volume (cm³)	X Y Z Coordinates (mm)	t-statistic	Approximate Anatomical Location
oxyHb	587 / 14.6	-18 -103 -3	4.19	Cuneus / Lingual Gyrus (BA18)
deoxyHb	321 / 8.0	-18 -103 -3	4.55	Cuneus / Lingual Gyrus (BA18)
totalHb	455 / 11.4	-15 -103 -3	3.19	Cuneus / Lingual Gyrus (BA18)

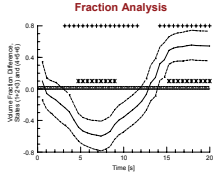
Statistical Significance of Time-Fraction Analysis

Comparison	Number of Voxels / Volume (cm³)	X Y Z Coordinates (mm)	t-statistic	Approximate Anatomical Location
State 2 vs. State 5	176 / 4.4	-21 -100 5	4.16	Cuneus / Middle Occipital Gyrus (BA18)
States (2+3) vs. State (5+6)	357 / 8.9	-26 -83 19	9.2	Middle Occipital Gyrus (BA18)
States (1+2+3) vs. State (4+5+6)	62 / 1.5	-26 -80 16	3.54	Middle Occipital Gyrus (BA19)

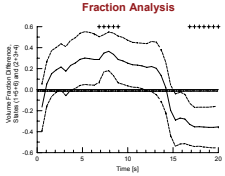
States (2+3) vs. (5+6) Volume Fraction Analysis



States (1+2+3) vs. (4+5+6) Volume Fraction Analysis



States (1+5+6) vs. (2+3+4) Volume Fraction Analysis



II. Resting State Study

Sensing Array Geometry: Sparse array of 30 source x 30 detectors. Approximately 2.5 cm spacing using International 10-20 System.

Instrumentation: DYNOT 232 fNIRS tomography system (NIRx Medical Technologies, Glen Head, NY). Image framing rate ~ 2 Hz.

Protocol: Subjects asked to stare at an otherwise blank screen containing a "+" figure for 10 minutes, while trying not to engage in active thoughts. Ages 23-41, 6M.

Data Analysis: Dual-wavelength measurements evaluated using modified Beer-Lambert Law to compute Hb_{oxy}, Hb_{deoxy}, Hb_{total} values for sensing channels.

Computed Metrics: Positional and time-dependent amplitude measures of central tendency; cross covariance values for original Hb time series and Hb State time series.

Hypothesis: The information content of ROIs that share common tissue-vascular coupling responses as revealed by covariations in Hb components is distinct from that identified by examination of its individual components. Examination of these can serve to reveal useful indicators of the phenomenology of resting states and regions of focal/coordinated activation.

RESULTS

Visual Activation Study

1. Volume of activation ranges from 8 – 14 cm^3. Significant activation seen in all three Hb components. Activated region identified across all nine subjects is localized to occipital cortex (cuneus/ Lingual gyrus (B-18)).

2. Time-fraction analysis revealed that difference in State 2 – State 5 is positive (negative BOLD response), significantly different from zero, and occurs in a region having almost no spatial overlap with activated region seen for single component analysis method. Similar results were seen for other listed combinations.

3.Time-dependent volume fraction analysis shows significant variations relative to zero (*) and baseline values (+), corrected for multiple comparisons.

Resting State Study: Preliminary Findings

1.Fourier spectra of spatial mean time series for combinatorial states reveals power spectra containing features not present in single Hb component spectra.

2. Amplitude of spectral components varies among the combinatorial states, by up to a factor of 4 in many cases.

3. Spatial distribution of cross covariance for single component Hb analysis reveals patterns that differ markedly from spatial patterns seen for individual Hb components.

4. Findings similar to (3) are seen in topographic amplitude maps, strongly suggesting that observed features are sensitive to different driving mechanisms.

SUMMARY

Examination of co-variations in the spatiotemporal behavior of Hb components that share common tissue-vascular coupling behaviors produces features that are not revealed from consideration of behaviors of the individual Hb components. Characterization of these features can serve as markers for disease and as a basis for establishing enhanced interpretative strategies applied to the control of assistive devices.

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