Spectral Changes in the Brain Hemodynamic Response Measured by functional Optical Imaging during Single-Trial Events

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Abstract

Hemodynamic responses of brain during single-event trials to an odd-ball experiment are measured by functional optical imaging (fOI) method. The responses are divided into three 10 minute intervals and the periodograms of these segments are calculated. An increase in the power of 0.08-0.15 Hz range has been observed that correlate with the delayed behavioral response of subjects.

1. Introduction

Brain's physiological responses during prolonged cognitive engagement protocols have been known to alter due to changes in the level of neuronal activation (habituation), switching the source of energy metabolism, saturation of blood flow and volume to a specific area.

Observing the functional changes of brain under stress or during various types of cognitive stimuli poses challenges in terms of spatial and temporal resolution as well as non-invasiveness and comfort. Several methods such as PET, fMRI, SPECT, EEG mapping, and optical methods using near-infrared light have been proposed to investigate the electrical and hemodynamical changes during these stimuli. The purpose of all these studies is to model how behavioral reaction correlates with physiological measurements; hence leading

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to an understanding of the dynamics of physiological activity underlying fatigue, boredom, attention/vigilance-loss and cognitive overload.

This paper will emphasize on the advantages of using optical methods in monitoring the hemodynamical changes of the brain that take place during neuronal activation.

A. Light-Tissue Interaction During Brain Activation

When the brain is stimulated, two types of physiological events occur that effect the optical properties of the brain tissues: 1) ones that occur at cell membranes and in the extracellular space (ECS) and 2) ones that are associated with neurovascular coupling within the vascular bed [1],[2]. We will discuss the effects of biochemical and physiological changes on optical signals during brain activation.

1. Neuronal Activity and Communication via Extracellular Space

Several hypotheses have been proposed in explaining the coupling of neuronal activity to cerebrovascular dynamics and energy metabolism. These hypotheses have been tested on animal and human studies using several imaging modalities like positron emission tomography (PET), functional magnetic resonance imaging (fMRI), indicator dilution methods and electrophysiologic mapping via needle electrodes as well as with intrinsic optical signals (IOS) and functional near infrared imaging (fNIR) [1],[2],[3]. The hypotheses regarding what is measured with optical methods depend on two assumptions:

1. A fast signal which has response times on the order of milliseconds that is related to the changes in the index of refraction at neuronal and glial cells due to activation. The refractive index changes due to the movement of ions across the membrane which precedes osmotic changes and cell swelling. Light scattering at the boundaries of the membranes are observed to occur almost in synchrony with the electrical signals recorded across the membrane [1],[4],[5],[7]. The optical signals are observed to

establish a linear coupling with the neuron's membrane potential [7] (See Figure 2).

2. A much slower response (on the order a few seconds) in optical properties of the tissues is observed with respect to stimuli. This response can be measured non-invasively with the near-infrared spectroscopy. There are two working hypotheses in explaining the changes observed by optical methods: a. A possible explanation to coupling between the neuronal activity and cerebral blood flow (CBF) and metabolic changes can be found in Magistretti's work on cultured astrocytes [9]. This hypothesis suggests that increases in neuronal activity stimulated by the excitatory amino acid transmitter glutamate result in relatively large increases in glycolic metabolism in astrocytes. The energy supplied through glycolysis in the astrocyte is used to metabolize glutamate to glutamine before being recycled to neurons (See Figure 3). The increase in glycolytic processing in astrocytes leads to a transient overproduction of lactate. The lactate then leaves the astrocyte and is taken up and oxidatively metabolized by neurons [2],[6],[9], [10],[11],[12]. The increase in glucose utilization linked to activation is observed to be linked to the activity of Na+/K+-ATPase. The hypothesis stated that increased external K+ caused depolarization of both postsynaptic processes and presynaptic terminals. Presynaptic depolarization of terminals evoked calcium-dependent synaptic transmission and the release of glutamate, which in turn further depolarized postsynaptic elements and caused further increases in external K+ [10]. Hence spreading depression (SD) was thought to be a propagating wave of high K+-induced glutamate release and depolarization. Besides the Na+/K+ pump activity, K+ homeostasis in the ECS is also maintained by three other mechanisms located in glial cells: (1) K+ spatial buffering, (2) KCl uptake, and (3) Ca2+ activated K+ channels[2]. Membrane mechanisms responsible for the transport of ions across the cell membrane are always accompanied by the movement of water thus affecting the cell volume and the size of ECS while causing shrinkage or swelling of neural cells including glia [2]. b. The local brain activity in neurons is shown to induce a local arteriolar vasodilation

and hence an increase in local cerebral blood volume (CBV) and CBF. The assumption and hypothesis under test is the contention on the use of CBF and CBV as an index of neuronal activity based on the concept of a tight coupling between neuronal functioning and local brain energy demand, and between local brain metabolic variations and CBF variations [8]. Monitoring of the CBF and CBV can be accomplished indirectly through a continuous monitoring of oxygenated and deoxygenated hemoglobin activity by near infrared light instruments [1]. Based on light absorption measurements, concentration changes of these molecules can be measured during functional brain activation, which leads to a computation of CBV and CBF [1],[6],[8]. The dynamic coupling of blood flow and oxygenation to neural function and metabolism is achieved by vasomotor action of cerebral arteries and arterioles. Increased neuronal activity, as seen in a higher frequency of action potentials, leads to the release of cellular K+ into the ECS. Since the ECS in the brain is small, and the intra/extracellular K+ concentration gradient high, a considerable increase results in the ECS K concentration, which in turn dilates the cerebral resistance vessels. This, together with the information forwarded by the action potential, result in quick adjustment of blood flow to the increased functional activity [17]. The original extra/intracellular distribution of ions then has to be reestablished on a long-term basis. Pumps are activated to carry K+ back into and Na+ out of the cells. Increased pump activity is accompanied by the increased metabolic activity. This is the basis for neuroimaging methods, which make use of the metabolic activity as an indicator of function. The signals for metabolically induced vasodilation, of which H and adenosine have been identified, continue to be released as long as a mismatch occurs between the oxygen/glucose demand and supply (See Figure 4). Vasodilation induced by these factors counteracts this mismatch and thus permits a fine-tuning of adequate blood supply to the tissue. Hence it is fair to assume that neuronal activity is directly coupled to cerebral blood flow. This direct coupling is mediated by K^+ ions, which are released from the neurons into the extracellular space of the brain resulting in increased extracellular K^+ concentration.

The increase in K^+ induces a vascular dilation in the region of increased neuronal activity without any time delay. In an idealized capillary tissue cylinder in the brain, an increase in blood flow in excess of the increased oxygen metabolic demands of the tissue is required to maintain proper oxygenation of the tissue. This conclusion originates from the limited diffusivity and poor solubility of oxygen in brain tissue. In this theory, blood flow remains coupled to oxidative metabolism but in a nonlinear fashion. Large increases appear to overcome the diffusion and solubility limitations of oxygen in brain tissue to maintain adequate tissue oxygenation.

B. Summary: What does fNIR measure and Can it be useful in functional activation studies?

Light shone into the tissue in the range of near infrared (700-900 nm) penetrates deep into the tissues up to 4 cm. Photons at this wavelength can travel deep due to the decreased absorbance of water. A typical set-up for probing the optical properties of tissues requires a light source and a detector placed either on the same surface for reflectance method or on the other side of the tissue for transmission method. Photons undergo mainly two types of interactions in the tissues: 1) Absorption and 2) Scattering (Chance et al., 1998; Obrig et al., 2000a; Obrig et al., 2000b; Villringer and Chance, 1997). Absorption effects are usually greater than scattering effects in tissues, hence the loss of photons become the limiting factor in detectability and sensitivity analysis. The main absorbers in the near infrared region are the oxygenated and deoxygenated Hemoglobin molecules, HbO_2 and Hb, respectively. The main scatterers are the denser cell organelles like the mitochondria, nucleus, cell membrane, endoplasmic reticulum and etc. (See Figure 1).

FIGURES

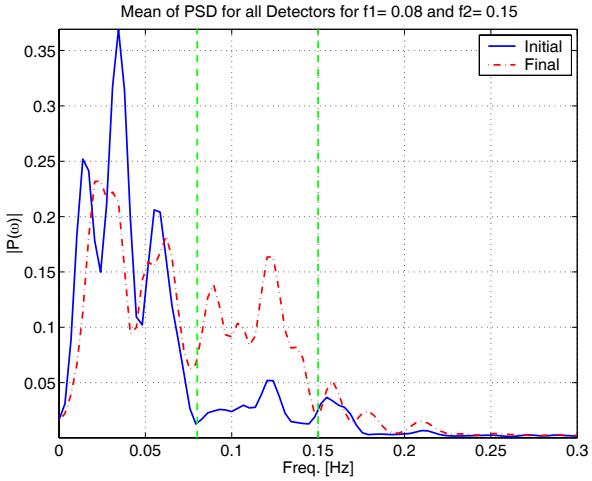
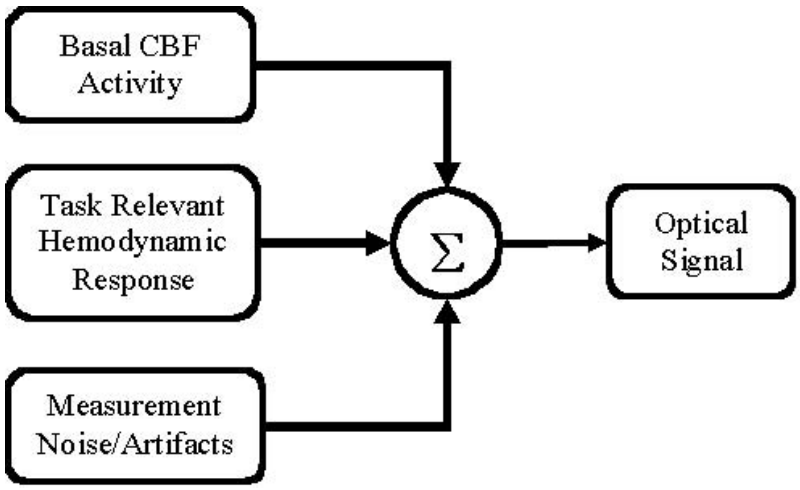
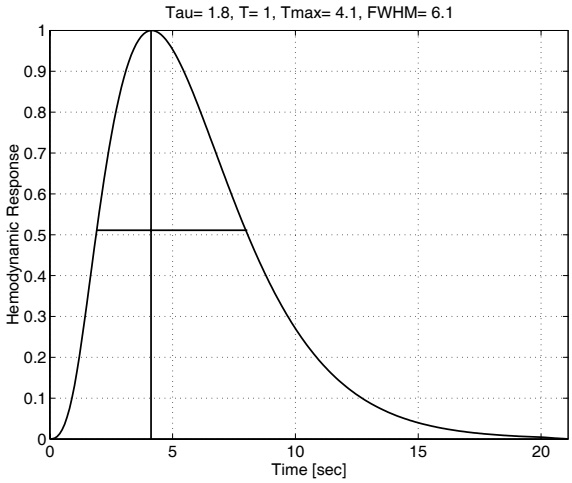


Fig. 1. Graphical representation of neurovascular coupling

Several studies have validated the use of fNIR during functional activation of the brain (For review, see (Chance et al., 1998; Obrig et al., 2000b; Villringer and Chance, 1997). The results indeed confirmed that fNIR best shows the response pattern of a deoxy-Hb decrease and an oxy-Hb increase when located over the area with the maximal BOLD-signal increase. Hence, the coupling of neuronal activation to blood flow and oxygen delivery can be monitored on a millisecond basis with the fNIR systems that use multi-wavelength illumination to extract both oxy-Hb and deoxy-Hb concentration changes (Boynton et al., 1996; Obrig et al., 2000a; Obrig et al., 2000b).



(a)



(b)

Fig. 2. (a) Signal components comprising the brain hemodynamic response. (b) A gamma function representation of brain hemodynamic response (Task-relevant response) to a single event lasting only $T = 500$ miliseconds.

C. Modeling Brain Hemodynamic Response

A common signal processing method used in the analysis of evoked responses is the Linear Time Invariant (LTI) systems approach. LTI approach assumes that the output of a

system can be calculated by convolving the impulse response of the system, $h(t)$, with the stimulation signal, $x(t)$:

$$y(t) = h(t) * x(t) \tag{1}$$

where $h(t)$ is considered to be the task-relevant signal in Figure 2(a) with a shape resembling a gamma function seen in Figure 2(b) while $x(t)$ is the total duration of the stimulus represented by a rectangular pulse with a duration of T. In our study, $x(t)$ stands for the duration that the target or the oddball stays on the screen (500 ms). The gamma function representation of the brain hemodynamic response has been adopted by several researchers in the fields of fNIRS and fMRI (Boynton et al., 1996; Calhoun et al., 2001; Obrig et al., 2000a; Villringer and Chance, 1997; Wobst et al., 2001). We used a simplified version of this function as in 2 to be able to apply nonlinear regression analysis explained later:

$$h(t) = Ct^{n-1}e^{-(\frac{t}{\tau})} \tag{2}$$

The goal of this study is to investigate the relationship between the behavioral response time (finger press reaction time) and the model parameters (C and τ) of brain's hemodynamic response measured by fOI modality. The motivation is to validate the use of fOI system for such protocols in places where portability and cost-effectiveness as well as comfort are required.

2. Methods

A. Data Acquisition Protocol

Target categorization[1] **or "Oddball task"** A simple discrimination task, or "oddball" paradigm, in which subjects are presented with two stimuli or classes of stimuli in a Bernoulli sequence in the center of the screen. The probability of one stimulus is less than the other (e.g.,

[1]Approved by Drexel University IRB

20% of trials for the "target" or "oddball" stimulus, versus 80% of trials for the "typical" or "context" stimulus); the participant's task is to press a button when they see the less frequent of the two events. Stimulus categories are varied, beginning with the letters "XXXXX" versus the letter "OOOOO." 1,024 stimuli are presented 1500 ms apart (total time, 25 minutes); a target"X" is presented on 64 trials, with a minimum of 12 context stimuli in between to allow for the hemodynamic response (Mccarthy et al., 1997). The subjects are asked to press the left button on a mouse when they see "OOOOO" and right button when they see the target "XXXXX." This timing parameter is used as the behavioral reaction parameter tracking the performance of the subjects. Four male subjects with an age range of 22-50 are recruited for the preliminary test.

B. Data Analysis

fNIRS data are collected by a system developed at Dr. Britton Chance's laboratory at University of Pennsylvania. The system houses a probe with four three-wavelength LEDs and twelve photodetectors. The probe is placed on the forehead and a sports bandage is used to secure it on its place and eliminate background light leakage. Even at extreme care, there is always some noise present at the collected signals. The graphical representation of the fOI data seen in Figure 2(a) can be expressed mathematically as:

$$d_i(t) = y_i(t) + n_i(t) \tag{3}$$

where $d_i(t)$ represents the data recorded from the i^{th} detector, $y_i(t)$ is the real hemodynamic response modeled as Eq.2, and $n_i(t)$ is the noise present in the data. We have used an outlier elimination algorithm to eliminate particularly the movement artifacts with spikes (Pearson, 2002).

Once the detector data are cleaned, blood volume data and oxygenation data are calculated from the measured changes in the concentrations of oxygenated hemoglobin, $\Delta[\mathrm{HbO}_2]$, and deoxygenated hemoglobin,Δ[Hb], by the following equations:

$$\Delta BV = \Delta[\mathrm{HbO}_2] + \Delta[\mathrm{Hb}] \tag{4}$$

$$\Delta OXY = \Delta[\mathrm{HbO_2}] - \Delta[\mathrm{Hb}] \tag{5}$$

We perform curve fitting to the gamma function, $h(t)$, the measured responses, $h_M(t)$, separately for BV and OXY data. This operation is performed by writing the measured response in a matrix form as:

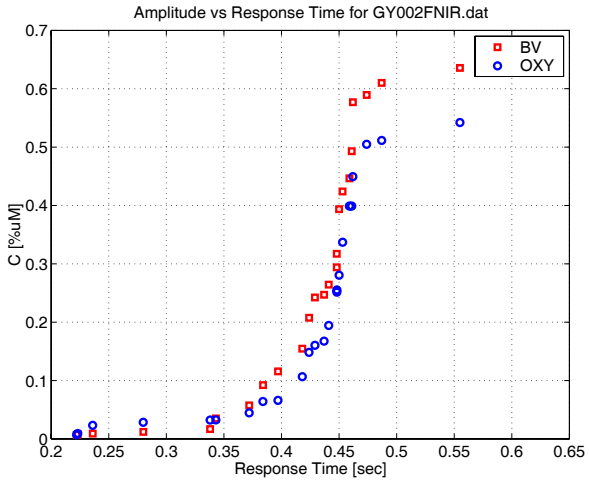
$$\mathbf{H_M} = \mathbf{T} \times \mathbf{A} \tag{6}$$

where $\mathbf{T} = [\,\mathbf{1}\ \ln \mathbf{t}\ \ \mathbf{t}\,]$ and $\mathbf{A} = [\,a_0\ \ a_1\ \ a_2\,]^{\mathbf{T}}$. Here $\mathbf{H_M}$ has a dimension of $1 \times N$; N denotes the total length of a single hemodynamic response (i.e. $N = 20$ points for our study), $a_0 = C$, $a_1 = n - 1$ and $a_2 = -1/\tau$. Simple matrix inversion yields the coefficients of the gamma function in Eq. 2:

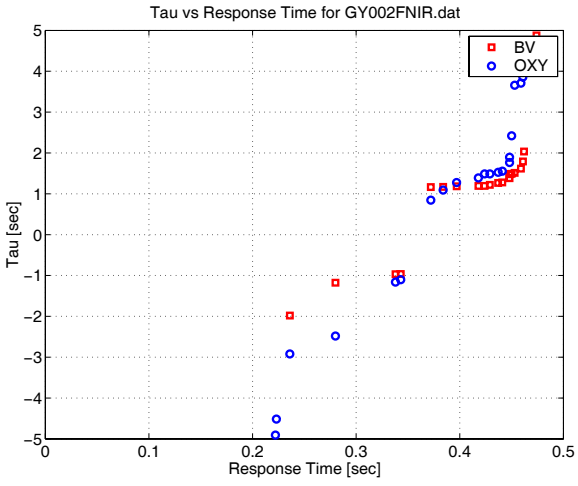
$$\mathbf{A} = \mathbf{T}\mathbf{H}_{\mathbf{M}}^{-\mathbf{1}} \tag{7}$$

3. Results

We observed the change in C and τ and plotted them against the finger press reactions (physiological response vs. behavioral reaction) as in Figures 3(a) through 4(b). Here we present the results of the two subjects. Due to a concern in preserving the intra-subject variability, subjects data are not lumped for C and τ vs. behavioral reaction parameter.

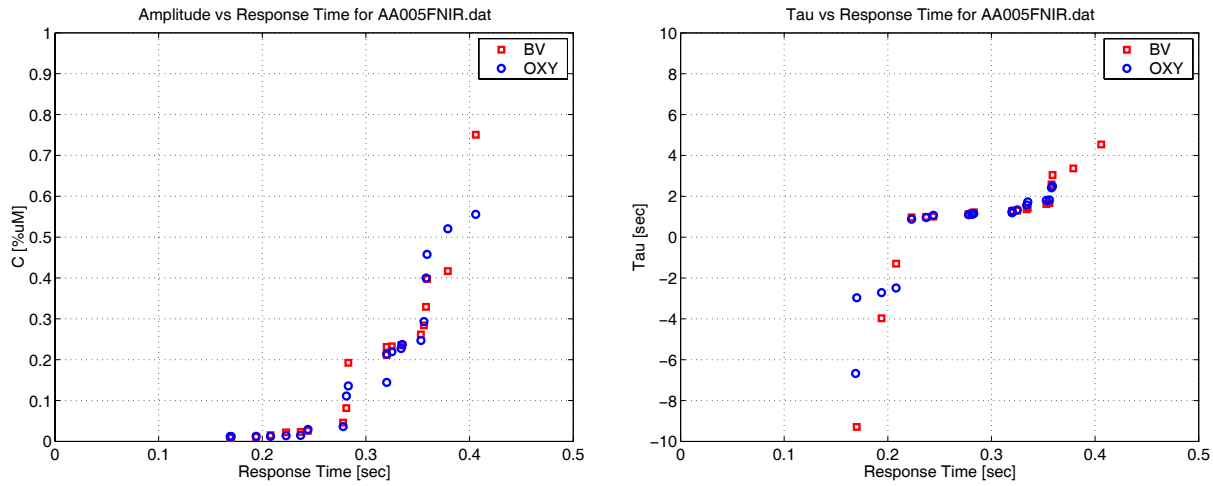


(a)



(b)

Fig. 3. (a) C amplitude vs behavioral reaction (b) τ vs behavioral reaction for subject GY.



(a) (b)

Fig. 4. (a) C amplitude vs behavioral reaction (b) τ vs behavioral reaction for subject AA.

4. Discussions and Conclusions

We have compared the change in the amplitude (C) and time constant (τ) constant of the brain hemodynamic response measured by functional optical imaging method during a target categorization task. Measured responses are fitted to a gamma function to estimate the C and τ values. There is a proportional relationship between these two parameters and the finger press reactions.

We conclude that as the finger press reaction is delayed an increase in the C and τ parameters observed similar to the findings of (Boynton et al., 1996).

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References

Boynton, G. M., Engel, S. A., Glover, G. H., and Heeger, D. J. (1996). Linear systems analysis of functional magnetic resonance imaging in human v1. *J. Neuroscience*, 16(13):4207–4221.

Calhoun, V., Adali, T., and Pearlson, G. (2001). Independent component analysis applied to fMRI data: A generative model for validating results. *Proc. IEEE*, pages 509–518.

Chance, B., Anday, E., Nioka, S., Zhou, S., Long, H., Worden, K., Li, C., Turray, T., Ovetsky, Y., Pidikiti, D., and Thomas, R. (1998). A novel method for fast imaging of brain function, noninvasively, with light. *Optics Express*, 2:411–423.

Mccarthy, G., Luby, M., Gore, J., and Goldman-Rakic, P. (1997). Infrequent events transiently activate human prefrontal and parietal cortex as measured by functional mri. *JOURNAL OF NEUROPHYSIOLOGY*, 77(3):1630–1634.

Obrig, H., Neufang, M., Wenzel, R., Kohl, M., Steinbrink, J., Einhaupl, K., and Villringer, A. (2000a). Spontaneous low frequency oscillations of cerebral hemodynamics and metabolism in human adults. *Neuroimage*, 12:623–639.

Obrig, H., Wenzel, R., Kohl, M., Horst, S., Wobst, P., Steinbrink, J., Thomas, F., and Villringer, A. (2000b). Near-infrared spectroscopy: does it function in functional activation studies of the adult brain? *Intrl. J. Psychophysiol.*, 35:125–142.

Pearson, R. K. (2002). Outliers in process modeling and identification. *IEEE Trans. Control Systems Techn.*, 10(1):55–63.

Villringer, A. and Chance, B. (1997). Non-invasive optical spectroscopy and imaging of human brain function. *Trends in Neuroscience*, 20(10):4435–4442.

Wobst, P., Wenzel, R., M. Kohl, H. O., and Villringer, A. (2001). Linear aspects of changes in deoxygenated hemoglobin concentration and cytochrome oxidase oxidation during brain activation. *NeuroImage*, 13:520–530.