SINGLE TRIAL HEMODYNAMIC RESPONSE ESTIMATION IN A BLOCK ANAGRAM SOLUTION STUDY USING fNIR SPECTROSCOPY

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ABSTRACT

Near infrared spectroscopy (NIRs) has shown great potential in examining functional brain activity during cognitive tasks by enabling the measurement of changes in the concentration of deoxygenated and oxygenated hemoglobin. It attracted great interest due to its portability, low cost, safety and non-invasiveness. In this paper, we present a novel single trial hemodynamic response estimation algorithm in an anagram solution study using functional NIRs (fNIRs). The temporal profile of the hemodynamic response to each single trial stimulus is estimated by minimizing the error between the oxygenation data measured by fNIRs and a linear model. In this technique no prior assumption on the amplitude, latency, or variance of the hemodynamic response is required other than its shape to be a γ function. Once the estimates of single trial hemodynamic responses gathered from the dorsolateral prefrontal cortex are obtained, the features such as maximum amplitude, rise time, etc. are extracted and compared for different difficulty levels of the test.

1. INTRODUCTION

Near infrared spectroscopy (NIRs) enables the measurement of changes in the concentration of deoxygenated hemoglobin (deoxy-Hb) and oxygenated hemoglobin (oxy-Hb) non-invasively during functional brain activation in human. The technology allows the design of portable, safe affordable, non-invasive and minimally intrusive monitoring systems. This makes NIRs suitable for the study of cognition related hemodynamic changes under many working conditions and in the field [1-3].

In principle, oxy-Hb and deoxy-Hb have characteristic optical properties in the visible and near infrared light range. Therefore, based on functional optical measurements, concentration changes of these molecules can be measured during functional brain activation. Biological tissues are relatively transparent to light in the near infrared range between 700-900nm [1]. This 'optical window' allows assessment of brain activity non-invasively. Using this technique, several types of brain functions have been assessed, including motor and visual activation, auditory stimulation and performance of cognitive tasks [1-3].

Typically an optical apparatus consists of a light source by which tissue is radiated and a light detector that receives light after it is interacted with the tissue it was radiated to. Photons that enter the tissue may undergo in principle to different types of interaction such as absorption and scattering. According to the modified Beer-Lambert law [1], the light intensity after absorption and scattering of the biological tissue is expressed by:

$$I = GI_o e^{-(\alpha_{HB}C_{HB}+\alpha_{HBO2}C_{HBO2})L} \quad (1)$$

where G is the constant attenuation, I_o is input light intensity, α_{HB} and α_{HBO2} are molar extinction coefficients of deoxy-Hb and oxy-Hb respectively, C_{HB} and C_{HBO2} are the concentrations of them and L is the photon path length.

In fNIR applications, we obtain the relative change of deoxy-Hb and oxy-Hb according to time using two different wavelengths. If the intensity measurement at an initial time is I_b (baseline), and at another time is I, the Optical Density (OD) change due to change in C_{HB} and C_{HBO2}, during that period is found as:

$$\Delta OD = \log_{10}\frac{I_b}{I} = \alpha_{HB}\Delta C_{HB} + \alpha_{HBO_2}\Delta C_{HBO_2} \quad (2)$$

If the measurements are done at two different wavelengths we can find ΔC_{HB} and ΔC_{HBO2}. Using the changes in the concentrations of deoxy-Hb and oxy-Hb, oxygenation and blood volume are determined as:

$$\begin{aligned} Oxygenation &= \Delta C_{HBO2} - \Delta C_{HB} \\ Blood\ Volume &= \Delta C_{HBO2} + \Delta C_{HB} \end{aligned} \quad (3)$$

Modeling the oxygenation data or the hemodynamic response is important for several reasons for example these models may lead to better statistical maps, or to the possibility of performing simulations with the model or more importantly they can allow the possibility to give a physiological interpretation of the model parameters.

There have been several studies in modeling the hemodynamic response in fMRI. Some models utilized FIR filters, some employed statistical methods such as Bayesian modeling, some only used mathematical model fitting to Gaussian, Poisson or γ type functions [4-9]. In this paper, we implemented the latest approach in

functional near infrared spectroscopy (fNIRs) data and assume that the hemodynamic response can be modeled by a γ type function.

It has been shown that the hemodynamic response evolves over a 10 to 12 seconds period even for brief stimulus of few seconds or less [8]. When the stimuli are presented temporally away from each other, one can obtain the corresponding hemodynamic response to each stimulus presented as an expected γ function. However in most cognitive studies (problem solving, working memory or attention tests) [2,9] the stimuli are presented much closer to each other then 10-12 sec. Especially in real life applications, we may not be able to arrange the presentation of stimuli as in laboratory conditions. Hence, in order to analyze the metabolic changes in the brain during cognitive tasks, there is a need to estimate the single trial hemodynamic functions where the stimuli overlap.

Even though the temporally extended nature of the hemodynamic response presents challenges to data analysis, rapidly presented trials that overlap in time can be separated. The basis of separation is the finding that sequential (or continuous) events summate in a 'roughly' linear fashion [8,9]. This means that, the effect of a neuronal event will be to further increase the existing hemodynamic responses even if the hemodynamic responses from preceding events have not completely decayed.

There is yet another challenge other than the rapidly presented stimuli in hemodynamic response estimation. It has been shown that hemodynamic response may vary in timing and amplitude across brain regions, cognitive task paradigms across and even within subjects [8,9]. These variations can occur across data sets within an individual for a given brain region, or across individuals for a given region, or across regions. This variance in the hemodynamic responses should be addressed in any model that attempts to estimate single trial hemodynamic responses.

In this study, our goal is to estimate each evoked hemodynamic response by only assuming that each single trial hemodynamic response is in the form of a γ function and the total oxygenation data is modeled by the linear summation of each evoked hemodynamic responses to the rapidly presented stimuli. We estimated each single trial by optimizing the error between the total oxygenation data from fNIRs measurements and our linear model. In this approach, we make no further assumptions on the amplitude or on the timing of the responses. We do not assume that the responses to same stimulus should be the same, which can not be guaranteed in a cognitive study due to the fact that subject's physiological conditions may change. Another aim of the present study is to evaluate the estimated hemodynamic responses and extract features that can quantify cognitive state of the subjects such as the maximum amplitude or the peak value of oxygenation activation and time to peak or response time.

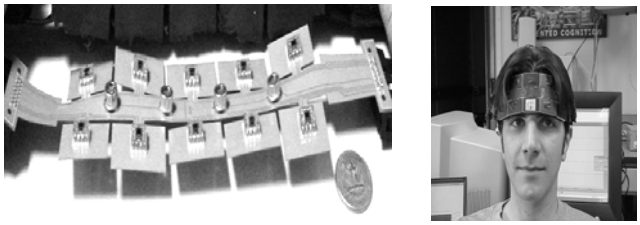
There have been continued studies in problem solving of graded difficulties (anagram solution) and it has been shown that a wearable NIRs measurement of metabolic activation and blood flow may be a useful educational aid [10]. The existing studies tested both block and event-related anagram protocols [10]. In event related anagram study subjects have to wait for 10-12 sec. for the presentation of the next anagram which not only increase the protocol time but also does not reflect a real world situation. In block anagram study, it was not possible to evaluate the subject's response times or brain activation for single anagram presentation within a block for graded difficulty analysis. In this study, by extracting the single trial hemodynamic response for each anagram letter in the block anagram study, we not only analyzed a more real world situation but also captured features such as maximum amplitude of the oxygenation activation and response time. We have shown that subjects needed more oxygenation and more time to solve the anagram as the difficulty of it is increased. The hemodynamic response estimates obtained by our algorithm reveal 0.92 correlation between the true and estimated response times.

In the next section, we present our signal collection device, fNIR probe, subjects we used in the protocols, the anagram solution protocol. In that section, we also explained our model and method to estimate evoked hemodynamic responses to each single event. In section 3 the results of our algorithm is discussed. Finally, we present the conclusion in section 4.

2. MATERIALS AND METHODS

2.A. fNIR Device

Our flexible fNIR probe has 4 light sources (LEDs) having 2 wavelengths of 730nm and 850 nm and 10 photo detectors separated from the sources by 3 cm as given in figure 1. Due to the placement and data collection arrangement of sources and detectors, we can collect 16 channels of data from the prefrontal cortex of the subjects [2]. The data is digitized by 4Hz sampling frequency.



(a) (b)

Figure 1 (a) fNIR Probe; (b) fNIR probe on a subject

2.B. Subjects

Informed consent statements approved by the institutional review board at University of Pennsylvania were obtained from fourteen neurologically normal subjects.

2.C. Anagram Solution Protocol

The protocol involves a scanning through anagrams of graded difficulty [10]. The protocol starts with a testing session. Then anagram blocks are presented on a computer screen containing sequences of three letter (3L), four letter (4L) and five letter (5L) anagrams starting from minimal (three letter anagrams) proceeding to the maximal level of difficulty (five letter anagrams) and then back down again to the starting point of three letter anagrams. Between each anagram block session, there is a rest period of 30 sec. Each anagram block is displayed for approximately one minute containing as many anagrams within depending on the number of processed anagrams by the subject. Whenever subjects solved the anagram they press a certain button on the keyboard, ('z') and whenever they can't they press another button ('/'). The decision of the subjects on each anagram processed and its timing is recorded on a text file for further analysis.

2.D. Hemodynamic Response Model

In this work, we model each single trial hemodynamic response by a γ function of the form:

$$hf(A,\alpha,\beta) = At^{\alpha}e^{\beta t} \tag{4}$$

where A is the amplitude. The parameters α and β change the rise time and fall time of the γ function. A typical γ function is given in figure 2.

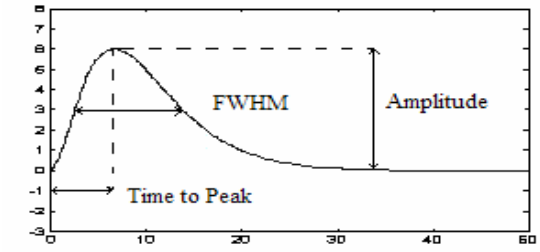


Figure 2: A typical γ function

Once the evoked hemodynamic responses are obtained for each single trial, the selective features such as amplitude, time to peak or full width half maximum (FWHM) can be used to assess subject's performance, cognitive state or attention for that particular trial. We will discuss these features, and their selective ability in the results section in more detail.

2.E. Model Fitting for Single Trial estimation

We assume that the oxygenation data that is measured by fNIR is formed by a linear model [8,9] where each hemodynamic response to N single trials or stimuli whether they are rapidly presented hence overlapping or not are added together to form the total oxygenation data, *Oxy* as given below:

$$Oxy = \sum_{i=1}^{N} hf_i \tag{5}$$

where hf_i is the evoked responses for ith stimulus presented at time t_i which is represented by a γ function with unknown parameters as follows:

$$hf_i = A_i t_i^{\alpha_i} e^{\beta_i t_i} \tag{6}$$

The unknown parameters (A_i, α_i, β_i) for all the N number of hemodynamic responses are found by minimizing the mean square error between the total oxygenation data, *Oxy* and the model by using a least mean squares curve fitting technique.

$$\varepsilon = \min_{A,\alpha,\beta}(Oxy - \sum_{i=1}^{N} hf_i)^2 \tag{7}$$

3. RESULTS AND DISCUSSION

For each subject and each anagram set of three, four and five letters, first the single trial evoked hemodynamic responses are estimated as γ functions and unknown parameters of A, α and β are optimized using the algorithm explained in section 2. As an example, measured *Oxy* (solid line), estimated *Oxy* (dashed line) and single trial hemodynamic estimates of one selected subject (subject 6) for a selected anagram block set (the 1st set of three letter anagram block) are presented in figure 3. All calculations are applied to 5th channel data which is gathered from the left hemisphere of the prefrontal cortex.

Note here that, in order to eliminate the relative measurement differences in oxygenation both within subjects (according to the baseline selection) and across subjects, we performed normalization on each subject's oxygenation data by scaling it to the interval [0,1]. This way, the differences between the anagram sets will still be active but affected only by a scale. Therefore in this study, we only compared the values of the features extracted from the single trial hemodynamic response estimates, i.e. the rise time and maximum amplitude, with respect to the difficulty level of anagram sets and the recorded values of subjects' response times.

By using the single trial hemodynamic response estimates, rise time (time to peak) and maximum amplitude averages of all the single trials are extracted for each subject and each anagram set. In the same manner response time averages for each anagram set and each subject that have been recorded during the data collection process are calculated. After outlier elimination, the averaged rise and response times and the maximum amplitude with respect to the anagram sets are presented in figure 4(a) and (b), respectively. It can be clearly seen that the estimated rise times follow the same pattern as the true response times of the subjects. The rise times and the maximum amplitude value increase as the difficulty level of the anagram solution increases meaning that subjects needed more time and more oxygen to solve difficult anagrams. The rise times drop a small amount in seconds (meaning subjects solve the anagrams faster than before) in the second set of anagram trials. This may mean that subjects get educated on how to solve the test. In figure 4(c) we present the scatter plot of the rise time versus response time for all subject anagram averages. This plot clearly shows that there is a correlation (correlation

coefficient=0.92) between the rise time estimates and the response times.

4. CONCLUSION

This paper presents a novel technique for the estimation of the single trial hemodynamic responses and extraction of reliable features for the assessment of cognitive activity in fNIR spectroscopy. The oxygenation data measured by the fNIRs is modeled using a linear model obtained by the summation of each evoked hemodynamic response to each stimulus and fitted to a γ function. The strength of this technique is that it does not make assumptions about the time parameters or equivalence of the hemodynamic responses, which may vary in studies of cognitive function. The model parameters for each evoked hemodynamic response are estimated by minimizing the mean square error between the linear model and the measured oxygenation data. The results of this procedure, tested in a problem solution paradigm with graded difficulty, namely anagram solution, are promising. The results demonstrate that single trial evoked responses and reliable features which can assess the cognitive activity, can be extracted from overlapping hemodynamic responses elicited by stimuli in close temporal proximity in a problem solution task.

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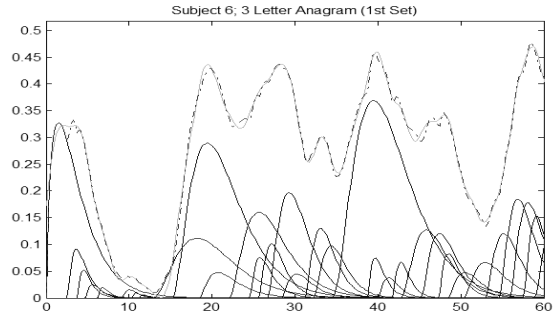
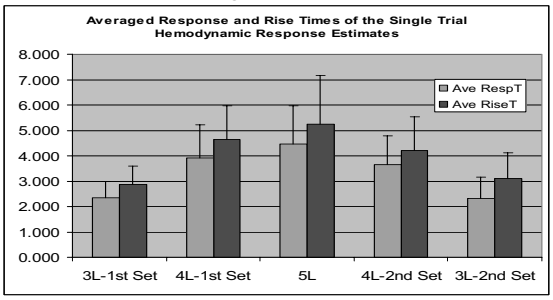
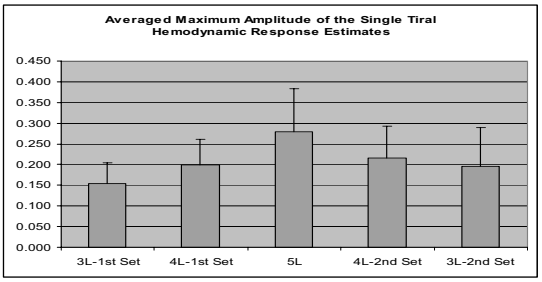


Figure 3: An example subject's (subject 6) *Oxy* data (solid line), estimated *Oxy* data (dashed line) and estimated single trials for the 1st set of 3 letter anagram block.



(a)



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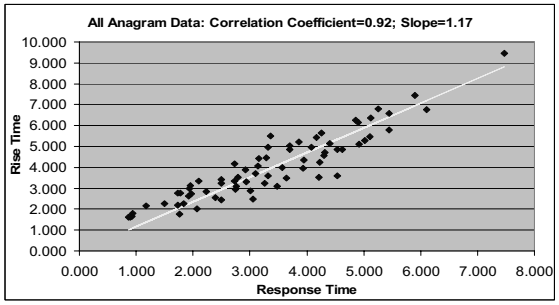

(c)

Figure 4: Subject averages of (a) rise and response times; (b) maximum amplitude; (c) Scatter plot of rise and response time averages for all anagram sets of all subjects