Nonlinear Estimation of Neural Processing Time From BOLD Signal With Application to Decision-Making

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Abstract: The extraction of information about neural activity timing from BOLD signal is a challenging task as the shape of the BOLD curve does not directly reflect the temporal characteristics of electrical activity of neurons. In this work, we introduce the concept of neural processing time (NPT) as a parameter of the biophysical model of the hemodynamic response function (HRF). Through this new concept we aim to infer more accurately the duration of neuronal response from the highly nonlinear BOLD effect. The face validity and applicability of the concept of NPT are evaluated through simulations and analysis of experimental time series. The results of both simulation and application were compared with summary measures of HRF shape. The experiment that was analyzed consisted of a decision-making paradigm with simultaneous emotional distracters. We hypothesize that the NPT in primary sensory areas, like the fusiform gyrus, is approximately the stimulus presentation duration. On the other hand, in areas related to processing of an emotional distracter, the NPT should depend on the experimental condition. As predicted, the NPT in fusiform gyrus is close to the stimulus duration and the NPT in dorsal anterior cingulate gyrus depends on the presence of an emotional distracter. Interestingly, the NPT in right but not left dorsal lateral prefrontal cortex depends on the stimulus emotional content. The summary measures of HRF obtained by a standard approach did not detect the variations observed in the NPT. *Hum Brain Mapp* 33:334–348, 2012. © 2011 Wiley Periodicals, Inc.

Key words: balloon model; genetic algorithm; prefrontal cortex; anterior cingulate gyrus; laterality

INTRODUCTION

The BOLD signal is primarily generated by an increase in hemoglobin oxygenation status related to neuronal

activity through a complex chain of hemodynamic and metabolic processes. One of the major objectives of fMRI is to make valid inferences about the underlying neuronal activity from the measured BOLD signal, which is called the hemodynamic inverse problem [Buckner, 2003]. In order to do so, most fMRI data analyses rely on estimating the amplitude of the evoked hemodynamic response function (HRF) using a general linear model (GLM) framework. Recently, the analysis of the shape of the HRF has been proposed as a way to extract further information about the timing of neuronal activity [Bellgowan et al., 2003; Lindquist and Wager, 2007]. In fact, modulations of stimulus duration on the order of tens of milliseconds produce measurable differences in the shape of BOLD curve [Grinband et al., 2008]. Ogawa et al. [2000] have shown

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that it is possible to use BOLD fMRI to study temporal characteristics of neural signals on a time scale of milliseconds, using a very specific study design aimed at exploring this property of the signal.

The three summary measures most commonly used to describe the shape of HRF are the amplitude itself, the time-to-peak and the width-at-half-maximum. The amplitude theoretically correlates with neuronal firing rate, the time-to-peak is presumably related to the latency of the neural activity and the width-at-half-maximum is thought to reflect the duration of neural activity. However, two issues challenge the interpretation of variations in HRF summary measures in terms of neural activity changes [Lindquist and Wager, 2007]: the complex nonlinear relation between the neural activity and BOLD signal and the power and accuracy of a given HRF model in capturing true changes in amplitude, time-to-peak (or latency) and width-at-half-maximum. Lindquist and Wager [2007] proposed a superposition of three inverse logit functions to model the HRF (IL model) and have shown that this model had the best performance for independent estimation of the HRF summary measures. Nevertheless, when using a fixed model of the HRF, the interpretability of HRF summary measures in terms of physiological parameters remains problematic mainly because of the nonlinear issues mentioned above.

In the present work, we introduce a method to infer the duration of neural activity from the BOLD signal. To achieve this objective, we have introduced the concept of neural processing time (NPT) as a parameter of a biophysical model of BOLD signal. The biophysical model implemented was the extended balloon model in which the cerebral blood flow was modeled by a harmonic oscillator differential equation [Buxton et al., 1998; Friston et al., 2000]. The neural activity is considered an external force to the oscillator model and is modeled as a boxcar function. In fact, a theoretical result derived from Pontryagin's minimum principle [Pontryagin, 1962] states that the on/off dynamics of neural signals are the natural solution of the hemodynamic inverse problem based in this very same biophysical model [Vakorin et al., 2007].

Nonlinear parameter estimation algorithms have been proposed as a way to approach the inverse hemodynamic problem [Riera et al., 2004; Vakorin et al., 2007; Wager et al., 2005]. Among these, the genetic algorithm is a reliable and relatively efficient method of estimation of the parameters of the highly nonlinear biophysical model of the BOLD signal [Vakorin et al., 2007]. Simulations using the genetic algorithm were performed in order to explore the face validity of this parameter estimation procedure. Simulations were also performed in order to clarify the relation between the NPT and the HRF summary measures calculated from the IL model. The estimation of the IL model HRF parameters was based in the simulated annealing algorithm as proposed by Lindquist and Wager [2007]. The main aim of these simulations was to verify whether NPT was a measure not derivable from any of

the HRF summary measures as these are the current standard for the inference of duration of neural activity from BOLD signal.

We chose a decision-making paradigm with simultaneous emotional distracters to test the applicability of the NPT concept. The task consisted of gender decision making in three experimental conditions: neutral faces (i.e., no emotional distracter), a mild sadness expression, and a high sadness expression. Previous fMRI studies with this experimental design have showed activation of fusiform gyrus (FG), dorsal anterior cingulate cortex (DACC), and dorsal-lateral prefrontal cortex (DLPFC) [Egner et al., 2007; Meriau et al., 2006].

The BOLD related neural activity in areas directly related to sensory processing of stimuli lasts until the end of their presentation [Logothetis et al., 2001]. By contrast, the duration of neural activity underlying decision-making or control of distracters is probably variable and is generally sustained up to the measured response time (RT). Assuming that the FG is primarily involved in the visual processing of faces, we predicted that the estimated NPT at FG would be similar to stimuli presentation time for all experimental conditions. However, in areas involved in decision-making we expected NPTs smaller than the stimulus duration and comparable to the RT. In DACC, supposedly engaged in control of emotional distracters [Kerns et al., 2004], we predicted that the NPT must depend on the emotional content of the stimuli.

Neural Processing Time (NPT) and the Neural-Hemodynamic Coupling

The seminal work conducted by Logothetis et al. [2001] has provided robust evidence for the neural basis of the BOLD signal. Their results have shown that the BOLD signal correlates better with local field potentials (LFP) than with multiunit activity (MUA). The LFP signal is sustained during the presentation of a stimulus in primary sensorial cortex and its duration is probably related to the RT in brain areas engaged in decision-making. Considering these characteristics of the LFP signal and since the time scales of the neural activation and deactivation are much smaller than that of the HRF, a boxcar function is a reasonable choice to model the BOLD signal related neural activity $u(t)$:

$$u(t) = \begin{cases} 1 & \text{if } \theta_i \leq t < \theta_i + \delta_i \\ 0 & \text{otherwise} \end{cases} \quad (1)$$

where θ_i is the time point of a given stimulus in the stimuli vector $\theta = (\theta_1, \theta_2, \dots, \theta_n)$, n is the total number of stimuli events, and δ_i is the NPT corresponding to the stimulus presented at time θ_i (see the left part of Fig. 1).

In order to model the relationship between regional blood flow and neural activity, Friston et al. [2000] have proposed the following system of differential equations:

Figure 1.

The biophysical model of NPT and BOLD signal. The biophysical model of the BOLD signal is an input-state-output dynamical system. The input is a vector of stimuli θ and the output is the variation of the magnetic signal or BOLD effect. The neural activity was modeled as a boxcar function with variable duration

$$\begin{cases} \frac{ds(t)}{dt} = \varepsilon u(t) - k_s s(t) - k_f (f(t) - 1) \\ \frac{df(t)}{dt} = s(t) \end{cases} \quad (2)$$

where $s(t)$ represents a vasoactive signal generated by the neural activity $u(t)$ that changes the regional cerebral blood flow $f(t)$. Since the parameter ε is simply a scaling factor of no great interest from a biophysical perspective [Friston et al., 2000; Stephan et al., 2007], it is assumed here to have unit value. The hemodynamic parameters k_f and k_s represent the time constants for cerebral blood flow $f(t)$ and vasoactive signal $s(t)$ decay, respectively.

The system of differential Eq. (2) can be rewritten as the single equation

$$\frac{d^2 f(t)}{dt^2} + k_s \frac{df(t)}{dt} + k_f f(t) = u(t) + k_f. \quad (3)$$

The Eq. (3) is a nonhomogeneous second-order differential equation that models a damped harmonic oscillator submitted to an external rectangular force $u(t) + k_f$.

The function $f(t)$ was used as the input to the balloon model producing the regional cerebral blood volume $v(t)$ and the deoxyhemoglobin content $q(t)$ as outputs. The modeled BOLD signal was obtained by a nonlinear algebraic equation with variables $v(t)$ and $q(t)$ (see Appendix). The forward hemodynamic model is summarized in Figure 1. Note that, given this model formulation, the inverse hemodynamic problem of estimating the NPT consists of finding the impulse function to the neural-hemodynamic coupling model that gives the best fit to the observed BOLD data. In other words, the problem is to find the set of parameters $\{\delta_1, \dots, \delta_n, k_f, k_s\}$ that minimizes the residues in modeling the temporal evolution of BOLD signal. In order to solve this inverse hemodynamic problem we used a genetic algorithm as explained in the next section.

The Eq. (3) is a nonhomogenous second-order differential equation and a general solution for this equation can

be written as a sum of analytical functions. A classical theorem states that the general solution of the second-order nonhomogeneous differential equation can be obtained from the sum of any particular solution and the solution of the corresponding homogeneous equation:

$$\frac{d^2 f(t)}{dt^2} + k_s \frac{df(t)}{dt} + k_f f(t) = 0. \quad (4)$$

The solution of the homogeneous Eq. (4) depends on the discriminant ω of the second-order polynomial described by the equation:

$$\omega = k_s^2 - 4k_f. \quad (5)$$

The general solution of the homogeneous equation is given by

$$f(t) = e^{-k_s t/2} [c_1 z_1(t) + c_2 z_2(t)]$$

$$\begin{aligned} z_1(t) &= \begin{cases} \cos(\sqrt{-\omega}t/2) & \text{if } \omega < 0 \\ 1 & \text{if } \omega = 0 \\ \exp(\sqrt{\omega}t/2) & \text{if } \omega > 0 \end{cases} \\ z_2(t) &= \begin{cases} \sin(\sqrt{-\omega}t/2) & \text{if } \omega < 0 \\ t & \text{if } \omega = 0 \\ \exp(-\sqrt{\omega}t/2) & \text{if } \omega > 0 \end{cases} \end{aligned} \quad (6)$$

where c_1 and c_2 are constants that are determined by the initial conditions of $f(t)$ and its first derivative. The functions $f(t)$ and $s(t)$ are defined as the relations to baseline value of the blood flow function $F(t)$ and the vasoactive signal $S(t)$, respectively ($f(t) = F(t)/F(0)$ and $s(t) = S(t)/S(0)$). Assuming that the baselines of $F(t)$ and $S(t)$ are non-zero, the initial condition are $f(0) = 1$ and $s(0) = 1$, by definition. The constants c_1 and c_2 are obtained by evaluating the linear system with two equations that results from

Figure 2.

Effects of parameter variation on the BOLD curve. The signal of $\omega = k_s^2 - 4k_f$ defines the behavior of the solution of Eq. (3). For $\omega > 0$, the solution is an overdamped harmonic oscillator. For $\omega = 0$, there is a critical behavior and for $\omega < 0$, solution of differential equation is equivalent to an underdamped oscillator. The modeled regional cerebral blood flow $f(t)$ is the solution of

Eq. (3). **(A)** The dependence of $f(t)$ on ω signals and the result of applying these function $f(t)$ in balloon model to produce a BOLD signal curve. **(B)** The effects of variation of the parameters of NPT and the hemodynamic parameters on modeled BOLD curve. Note that neither parameter has a linear or easily specified effect on the curve.

applying the initial conditions to Eq. (6). The general solution of the homogeneous equation for $\omega < 0$ corresponds to an underdamped oscillator, $\omega = 0$ represents critical oscillation dynamics and $\omega > 0$ models an overdamped harmonic oscillator (Fig. 2). We allowed k_f and k_s to assume values between 0 and 1, making no restriction on ω . Both time constants k_f and k_s cause important changes in the shape of the modeled BOLD signal as illustrated in Figure 2.

MATERIALS AND METHODS

Parameter Estimation

The estimation of the BOLD biophysical model parameters is crucial for the application of the model in experimental studies. Nevertheless, this model has a large number of parameters and high degree of nonlinearity, which presents difficulties for statistical analysis [Vakorin

et al., 2007; Wager et al., 2005]. All parameters of the biophysical model except the NPT and the parameters of the neuro-hemodynamic coupling (k_f and k_s) were fixed (see the previous section and Discussion).

Given a BOLD time series and the stimulus onsets, parameter estimation consists of computing the set of parameters $\{\delta, k_f, k_s\}$ that best describes the signal evolution through time. Assuming that the NPT depends on the experimental condition, the set of parameters is $\{\delta_1, \dots, \delta_K, k_f, k_s\}$ for K conditions. In other words, the aim is to find the parameters that minimize the sum of squares error between the expected HRF convolved with the vector of stimuli and the observed BOLD signal. However, this optimization problem is not trivial, mainly due to the intrinsic model nonlinearities. Stochastic optimization methods such as genetic algorithms [Kjellstrom, 1996] are useful in such cases, in order to avoid problems with local minima. We thus suggest the following approach to resolving the optimization problem (Fig. 3):

$$\min_{\delta_1, \dots, \delta_M, k_f, k_s} \text{SSQ}(\delta_1, \dots, \delta_M, k_f, k_s), \quad (7)$$

where SSQ is a function defined by the following steps

1. Step 1: Build a binary stimuli vector (0 for baseline and 1 for condition);
2. Step 2: Generate the HRF by using the extended balloon model with NPT and hemodynamic parameters as free parameters ($\{\delta_1, \dots, \delta_K, k_f, k_s\}$), choosing a plausible set of initial values in the first iteration;
3. Step 3: Convolve the vectors of stimuli with their respective HRFs, obtaining the predictors for the general linear model;
4. Step 4: Estimate the general linear model parameters (note that this step only rescales the predictors)
5. Step 5: Calculate residual sum of squares (SSQ);
6. Step 6: A new solution of the biophysical model is obtained by random specification of the free parameters in the framework of the genetic algorithm, returning to step 2.

The steps above define the target function to be minimized with the genetic algorithm. The genetic algorithm randomly iterates a group of parameters sets over the target function in order to achieve the lowest value of target, avoiding local minima. A group of parameters vectors that maximizes “fitness” (minimizes the target function) in each iteration is stochastically selected to “reproduce,” i.e., generate a new parameters population in next “generation” of parameters sets. Besides the target function, the parameters of the genetic algorithm include the start value (defined in step 2, only for the first iteration), the thermal noise (the variability of the new pseudorandomly generated sets of parameters), the number of iterations and the number of samples (“gene pool”) per iteration. The genetic algorithm was implemented in R using the gafit package (available at: <http://cran.r-project.org/web/packages/gafit/index.html>).

Figure 3.

Parameter estimation procedure. The HRFs were obtained by numerical solution of the biophysical forward model, given the set of parameters $\{\delta, k_f, k_s\}$. For the inverse problem approach, the residuals of GLM were minimized using a genetic algorithm.

Note that the procedure proposed is basically a nonlinear regression based on genetic algorithm and the General Linear Model (Fig. 3).

Simulations

To test the face validity of the parameter estimation procedure, we performed simulations for a representative set of parameters values. Figure 5 shows the results of the simulations of a set of parameters representative of the three possible dynamics of the neural-hemodynamic coupling [Eq. (5) and Fig. 2] with reasonable values of NPT for typical event-related experiments ($\{\delta = 1, 1.5, 2, 2.5, 3, 5 \text{ s}; k_f = 0.4; k_s = 0.65\}$, $\{\delta = 2 \text{ s}, k_f = 0.16; k_s = 0.99\}$, $\{\delta = 2 \text{ s}, k_f = 0.16; k_s = 0.8\}$). The parameters used in the other simulations are shown in Table I, which summarizes these simulation results. A “real” time series was constructed for each set of parameters by adding a Gaussian noise to the numerical solution of the biophysical model. The signal-to-noise ratio of the simulations shown is about 0.5, consistent with a typical 1.5 T fMRI experiment. We also performed simulations with SNR as low as 0.125 with reliable results (data not shown).

The “real” time series were then submitted to the genetic algorithm procedure described above. Besides the initial conditions of the parameters vector $\{\delta_1, k_f, k_s\}$, the number of iterations, the number of samples at each iteration or “gene pool” and the thermal noise must be specified in the genetic algorithm. For the simulation studies, the number of iterations was a hundred, the number of samples at each iteration was 10 and the thermal noise, that reflects the variability of the new “generations” of solutions, was 0.3. A thousand simulations were implemented for each set of parameter values. All the simulations were performed on an Intel Pentium Core 2.66 GHz processor and the forward

TABLE I. Results of simulations

$\delta = 1.0$								
k_s								
0.2			0.65		0.8		0.99	
k_f	0.16	δ	1.660 ± 1.41	1.374 ± 1.14	1.201 ± 0.98	1.054 ± 0.99		
		k_f	0.179 ± 0.08	0.186 ± 0.09	0.174 ± 0.06	0.156 ± 0.08		
		k_s	0.289 ± 0.12	0.739 ± 0.15	0.849 ± 0.15	0.931 ± 0.14		
	0.4	δ	1.138 ± 0.84	0.983 ± 0.78	1.176 ± 0.84	0.931 ± 0.76		
		k_f	0.410 ± 0.07	0.403 ± 0.11	0.430 ± 0.12	0.375 ± 0.10		
		k_s	0.234 ± 0.11	0.648 ± 0.15	0.832 ± 0.14	0.920 ± 0.13		
	0.8	δ	1.054 ± 0.73	1.015 ± 0.67	0.952 ± 0.57	0.890 ± 0.61		
		k_f	0.806 ± 0.09	0.811 ± 0.12	0.792 ± 0.13	0.746 ± 0.14		
		k_s	0.219 ± 0.12	0.645 ± 0.13	0.780 ± 0.15	0.894 ± 0.14		
$\delta = 2.0$								
k_s								
0.2			0.65		0.8		0.99	
k_f	0.16	δ		2.185 ± 1.25	2.075 ± 0.91	2.215 ± 1.12		
		k_f	NS	0.176 ± 0.08	0.158 ± 0.09	0.152 ± 0.08		
		k_s		0.679 ± 0.16	0.789 ± 0.17	0.929 ± 0.17		
	0.4	δ		2.215 ± 0.96	2.007 ± 0.86	1.820 ± 0.96		
		k_f	NS	0.405 ± 0.09	0.402 ± 0.11	0.355 ± 0.11		
		k_s		0.644 ± 0.12	0.788 ± 0.14	0.895 ± 0.14		
	0.8	δ		1.981 ± 0.78	1.943 ± 0.80	1.798 ± 0.85		
		k_f	NS	0.784 ± 0.13	0.773 ± 0.14	0.699 ± 0.16		
		k_s		0.620 ± 0.12	0.756 ± 0.13	0.879 ± 0.15		
$\delta = 5.0$								
k_s								
0.2			0.65		0.8		0.99	
k_f	0.16	δ		4.388 ± 1.93	4.222 ± 1.78	4.000 ± 1.75		
		k_f	NS	0.162 ± 0.09	0.158 ± 0.08	0.143 ± 0.10		
		k_s		0.624 ± 0.17	0.713 ± 0.19	0.804 ± 0.20		
	0.4	δ		4.774 ± 1.25	4.818 ± 1.44	4.382 ± 1.51		
		k_f	NS	0.385 ± 0.13	0.381 ± 0.15	0.326 ± 0.14		
		k_s		0.631 ± 0.15	0.752 ± 0.13	0.847 ± 0.15		
	0.8	δ		4.805 ± 1.01	4.668 ± 1.13	4.527 ± 1.17		
		k_f	NS	0.748 ± 0.15	0.715 ± 0.17	0.645 ± 0.19		
		k_s		0.639 ± 0.13	0.752 ± 0.14	0.866 ± 0.15		

Results of a thousand simulations for each set of parameters $\{\delta, k_f, k_s\}$. The expected results for k_f are in the first column and the expected results for k_s are in the first row. The mean and standard deviation value of each estimated parameter are shown. NS, there is no solution of the differential equations.

differential equations solutions and genetic algorithm were implemented in the R platform.

In order to compare the measure of the NPT based in the biophysical model and genetic algorithm with a standard inference of neural activity duration from the BOLD signal we used the IL model of the HRF. The simulated annealing algorithm was used to estimate the IL model parameters, avoiding local minima issues [Lindquist and Wager, 2007]. The HRF amplitude, time to peak and width-at-half-maximum were calculated for simulated time series generated through the biophysical model. Four different values of NPT ($\{\delta = 2, 5, 10, 20 \text{ s}; k_f = 0.4; k_s = 0.65\}$) were

simulated. The objective of these simulations was to clarify the relations between the NPT and the summary measures of HRF obtained through the IL model. These simulations were performed in MATLAB® and the software developed by Lindquist and Wager [2007] was used (available at: <http://www.columbia.edu/cu/psychology/tor/>).

Application to Experimental Data

The functional anatomy of emotional processing probably differs between male and female subjects. For example, lateralization of emotional processing seems to be

Figure 4.

Experimental design. Eighteen healthy right-handed male subjects performed gender recognition on faces. Faces with no emotional expression (black), and with intermediate (dark grey) and high (light grey) levels of sadness were presented according to a Poisson distribution (mean ISI of 5 s) for 2 s each, as illustrated at the lower part.

stronger and more consistent in men [Wager et al., 2003]. Considering these literature findings, we chose to include only male subjects. Eighteen right-handed volunteers (ages 57 ± 7 yr) with no history of significant medical, neurological, or psychiatric disease participated in the study. Subjects had normal or corrected-to-normal vision. The local ethics committee approved the study protocol (Project number CAPEPesq 414/03).

We applied an event-related paradigm involving gender recognition of faces in which the level of sadness was a distracter (Fig. 4). The paradigm included three experimental conditions: Eckmann's faces with low and high intensities of sadness and neutral faces, i.e., a control condition without concomitant distracter. The baseline presentation was a crosshair fixation. The presentation duration for each face was constant (2 s). The inter-trial interval was randomly varied according to a Poisson distribution (2–12 s; mean 5 s). This stimulus presentation scheme minimizes the nonlinearities observed for superimposed hemodynamic responses [Buckner, 1998].

The subjects were instructed to choose whether the presented face was male or female by a button press using the right hand. Reaction times and answers were recorded. Stimulus presentation was synchronized with the scanner via an optical relay triggered by a radio-frequency pulse

(Zurc & Zurc, São Paulo, Brazil). All images were acquired in a 1.5 T GE scanner, equipped with a 33 mT/m gradient. The images were oriented with the AC-PC line, and 15 slices with 7 mm slice thickness (0.7 mm gap) were acquired. A total of 168 brain volumes were acquired, 64×64 pixels, 20×20 mm FOV, flip angle 90° , TR 2.0 s, TE 40 ms, gradient echo EPI acquisition.

Image processing and brain activity mapping were carried out using the free software XBAM (available at: www.brainunit.co.uk), developed at the Centre for Neuroimaging Sciences, King's College London. All volumes were preprocessed by slice timing correction, motion correction (rigid body registration), spatial smoothing (FWHM = 9 mm) and spatial normalization to the stereotactic space of Talairach and Tournoux [Talairach, 1988]. The individual mapping was based on the General Linear Model (GLM), with the hemodynamic response function modeled using two Poisson functions with peaks at 4 and 8 s after stimulus onset. The group statistical significance was evaluated nonparametrically using permutation testing [Brammer et al., 1997; Nichols and Holmes, 2002].

The average time series of each subject for the activated clusters corresponding to FG, DACC and left and right DLPFC were extracted using the XBAM software. These time series were then submitted to our parameter

estimation procedure. The NPT was allowed to vary between brain regions and experimental condition but not within the same experimental condition. This is reasonable since the duration of stimuli presentation was constant.

The parameters used in the genetic algorithm were as follows: 1,000 iterations, 50 samples at each iteration, a thermal fluctuation of 1, initial $k_f = 0.4$, initial $k_s = 0.7$, initial $\delta_1 = \delta_2 = \delta_3 = 2.5$. The algorithm was implemented in R using the *gafit* and *lsoda* packages.

The same time series were also submitted to the simulated annealing algorithm with the IL model in order to estimate the HRF summary parameters for each experimental condition. These analysis were performed with the MATLAB[®] algorithm developed by Lindquist and Wager [2007].

The genetic algorithm produced one measure for each biophysical model parameter (δ_1 , k_f , and k_s), each subject, each ROI and each experimental condition (emotional content on face). The Wilcoxon signed-rank test was used to compare the distribution of each parameter between the experimental conditions. Analogously, the simulated annealing algorithm results in one number for each HRF (IL model) summary measure (amplitude, time-to-peak, and width-at-half-maximum) and the same statistical test was used to compare the distributions between experimental conditions.

RESULTS

Simulations

The results of the simulations are summarized in Table I and Figure 5. Five different values for NPT (δ) (1, 1.5, 2, 2.5, 3, and 5 s) were simulated in the results showed in Figure 5, demonstrating the method is suitable to estimate δ in the range expected for a typical event-related paradigm. The two sets of histograms in the bottom of Figure 5 show the results for simulations with NPT of 2 s and the critical and over damped dynamics of the neural-hemodynamic coupling model. Table I shows the results of simulations for three values of NPT (1, 2 and 5 s) and three values

Figure 5.

Simulations results. Each row with three histograms represents the result of thousand simulations, the horizontal axis being the estimated parameter and vertical axis being the density of values. Black vertical lines represent the real values of the parameters. Each row shows results of simulations for a particular set of parameters, the first five rows illustrating the results of simulations with k_f and k_s fixed ($k_f = 0.4$, $k_s = 0.65$), varying the values of time δ (1, 1.5, 2, 2.5, 3, and 5 s). The two last rows are results of simulations for a fixed value of time (2 s) and varying values of k_f and k_s , covering the two other possible behaviors of the harmonic oscillator model. The last row shows the results for positive ω and the anterior for null ω . In the critical dynamics of oscillation model, there was greater variation of the estimated values of the hemodynamic parameter k_s . Despite this error in the estimation of k_s , good estimations of k_f and NPT were obtained, guaranteeing the confidence of the procedure even in this particular case. The results of all simulations are summarized in Table I.

Figure 6.

Results of simulations of simulated annealing algorithm with three superposed inverse logit functions HRF. The three summary measures of HRF shape obtained by the simulated annealing algorithm with a three superposed inverse logit functions HRF were accessed for a range of neural processing time values. Note that the variation on NPT affects all the three parameters (high confusability), which compromises the interpretability of these measures.

of hemodynamic parameters covering the physiologically plausible range and all combinations of these parameters.

Between 7 and 15 runs per thousand simulations did not converge due to numerical problems or singularities. These values were not included in the construction of histograms represented in Figure 5 and in the calculation of the values of mean and standard deviation in Table I. In Figure 5, note that unimodal peaks of estimated values were close to the parameters of the real curve. In Table I, the NS (No Solution) tag represents combinations of the hemodynamic parameters that not have a corresponding real solution of the forward model. Table I shows that the mean NPT is under or overestimated only for extreme values of hemodynamic parameters, which probably do not correspond to a plausible physiological condition. In general, these simulations have shown that the genetic algorithm works well for the specific optimization problem proposed with a realistic signal-to-noise ratio, offering an empirical evaluation of the validity of the method for the estimation of parameters in real fMRI data.

In order to clarify the relationship between the summary measures of the IL model HRF and the NPT we applied the simulated annealing algorithm to “real” time series constructed from the biophysical model of BOLD signal. In these simulations we varied only the NPT, fixing the hemodynamic parameters. The results of these simulations are represented in Figure 6.

All the three HRF parameters vary with the NPT in a nonlinear manner. In fact, the variation of time-to-peak with NPT was not monotonic. Besides this, the variance of the estimated amplitude of HRF for NPT of 2 s was remarkable high. For width-at-half maximum it was observed that the histograms for NPT of 10 s or less were superposed. These findings illustrate the high confusability of the three param-

eters of HRF, i.e., a change in a single physiological parameter affects all the HRF parameters. It also shows the poor correlation between width-at-half-maximum and NPT. Figure 2B shows HRFs calculated directly from the biophysical model for different NPTs. Visual inspection of these curves demonstrates the nonlinear relation between NPT and HRF amplitude, time-to-peak and width-at-half-maximum. These findings together indicate that direct inference of the duration of neural activity from variations in the parameters of the HRF was not possible. In addition, our findings are consistent with published reports of the difficulty of estimation of true changes in HRF summary measures [Lindquist et al., 2009].

Application to Experimental Data

The average reaction times and response accuracies for each subject were calculated (neutral faces—mean: 1,081.63 ms, SD: 305.62 ms, 92% right responses; mildly sad faces—mean: 1,033.87 ms, SD: 335.75 ms, 87% right responses; highly sad faces—mean: 1,079.73 ms, SD: 317.31 ms, 89% right responses). There were no statistically significant differences in these behavioral measures between the experimental conditions. The brain regions with significant main effects identified by voxel-wise analysis are listed in Table II. The regions of interest (ROIs) were defined as the four most activated clusters: the fusiform gyrus (FG), the dorsal anterior cingulate gyrus (DACC), the right and the left dorsal-lateral prefrontal cortex (DLPFC) (Fig. 6). The average time series of the four ROIs for each subject were submitted to the parameter estimation procedure.

The mean estimated values of the hemodynamic parameters k_f and k_s were summarized in Table III. The values of these hemodynamic parameters were similar to previously

TABLE II. Regions with significant main effect detected by voxel-wise analysis

Anatomical Region	Hemisphere	Brodmann area	Cluster size (voxels)	Coordinates (x, y, z)
Cingulate gyrus	L	BA 24	75	7, 0, 42
Precentral gyrus	L	BA 3/46	155	40, -15, 37
Precentral gyrus	R	BA 4/46	61	-29, -19, 48
Lingual gyrus	R	BA 19	72	-21, -59, -2
Precentral gyrus	R	BA 6	47	-40, -11, 37
Cuneus	L	BA 17	34	11, -89, 9

The four clusters with more activated voxels were the cingulate gyrus, right and left dorsal-lateral prefrontal cortex, and fusiform gyrus.

published results using several methods [Buxton et al., 2004; Deneux and Faugeras, 2006; Vakorin et al., 2007]. Note that the values for ω were consistently negative, suggesting an underdamped dynamic for the blood flow transient oscillation. The mean estimated NPTs as a function of the degree of sadness of the faces are shown for each ROI in Figure 7.

In the FG and the left DLPFC, the mean estimated NPT did not vary with the emotional content of the faces. Interestingly, the mean NPT in these brain areas was about 2 s for all the experimental conditions, exactly the same duration as that of stimulus presentation. The mean estimated NPT in the right DLPFC was significantly lower for sad faces than for neutral faces ($P < 0.05$). The variance of the NPT was greater for mild sad faces than for neutral faces in the right DLPFC. A significantly lower mean NPT for sad than for neutral faces was also observed at the DACC ($P < 0.05$). The mean estimated NPT for mild sad faces in the DACC lay between the values for neutral and sad faces, but these differences were not statistically significant.

Figure 8 shows the results of the summary measures of the HRF shape evaluated with the simulated annealing algorithm and IL model. There were no statistically significant differences for any of the measures for the three experimental conditions. This finding indicates that the estimation of summary measures of HRF shape could not reproduce the results obtained by the NPT estimation. The

modeled BOLD curves for each cluster are shown in Figure 9. Note that the differences in the HRFs estimated with the genetic algorithm and biophysical model are remarkable subtle, which may explain the failure of HRF model to capture variations in NPT.

DISCUSSION

The shape of the BOLD signal varies according to the spatial and temporal characteristics of the underlying neural activity. The HRF's time-to-peak and full-width at half-maximum have previously been suggested as measures of the duration of neural activity. However, these measures depend on the HRF model and on other variables such as signal amplitude, making it very difficult to recover the neural activity duration [Lindquist et al., 2009]. To overcome this difficulty, we propose a biophysical model with NPT as a parameter that is estimated using a nonlinear genetic algorithm based procedure. The method's ability to recover the parameters of the model from noisy data was extensively evaluated through simulations. The relationship between summary measures of HRF estimated with the simulated annealing algorithm and the IL model and the theoretical NPT as a parameter of the biophysical model of BOLD signal were also studied through computational simulations.

The genetic algorithm based method was also applied to experimental data producing estimated values of hemodynamic parameters consistent with the previous literature. Furthermore, the estimated NPT values were in agreement with our hypothesis on the function of the neural network accessed. Interestingly, the estimated summary measures of HRF shape could not reproduce the findings of variation of NPT with experimental conditions.

Despite these results, another set of difficulties and limitations is associated with the biophysical model approach to the hemodynamic inverse problem in comparison to HRF summary measures. The biophysical model is probably a nonidentifiable system, i.e., there is no unique solution for the inverse hemodynamic problem specified by the extended balloon model. To our knowledge, no satisfactory solution to this limitation has been proposed except for restriction of the number of parameters to be

TABLE III. Estimated values of hemodynamic parameters

	k_f			k_s			ω
	Mean	Median	SD	Mean	Median	SD	Mean
FG	0.411	0.417	0.139	0.600	0.614	0.182	-1.282
DACC	0.466	0.414	0.116	0.479	0.443	0.161	-1.633
Right DLPFC	0.387	0.370	0.196	0.544	0.468	0.200	-1.250
Left DLPFC	0.552	0.596	0.253	0.463	0.431	0.189	-1.995

The mean, median, and standard deviation of the estimated values of the parameters k_f and k_s for the four brain regions are shown. Note that the parameter $\omega = k_s^2 - 4k_f$ is consistently negative, suggesting an underdamped oscillator dynamics for the neural-hemodynamic coupling.

Figure 7.

Estimated neural processing times (NPT). Mean values of estimated NPT at the four ROIs analyzed (FG, dACC, right and left DLPFC) and for the three experimental conditions are shown. Dashed lines mark the time of each stimulus presentation (2 s) and red bars indicate significant differences in estimated NPTs (P values evaluated through the Wilcoxon test). In the FG and left DLPFC the NPTs for all experimental conditions were equal to the time of stimuli

presentation. Note that NPT was significantly lowered for sad than neutral faces at dACC and right DLPFC. Furthermore, the variability of estimated values was greater in right compared to left DLPFC, especially for faces with the intermediate level of sadness. These results show a functional lateralization of DLPFC. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

estimated at any one time. However, fixing parameters a priori imposes further potential sources of error on the estimated values. This is because not all hemodynamic sources of the BOLD signal variation are taken into

account when parameters are fixed. However, choosing a representative set of free parameters based on preliminary theoretical studies minimized the errors introduced by parameter fixation [Vakorin et al., 2007].

Figure 8.

Results of summary measures of HRF obtained by the simulated annealing algorithm with a three superposed inverse logit functions. Results of the application of a standard method of estimation of duration of neural activity from HRF to the experimental data showed no statistically significant differences for the experimental conditions.

Figure 9.

Estimated hemodynamic response functions (HRFs). The normalized values of cerebral blood flow $f(t)$, cerebral blood volume $v(t)$, deoxyhemoglobin content $q(t)$, and BOLD response (HRF) for the parameters estimated are shown.

The nonlinearities of the BOLD signal depend on stimulus presentation time and interstimulus interval [Birn and Bandettini, 2005; Birn et al., 2001; Vazquez and Noll, 1998; Yacoub et al., 2006]. We chose a stimulus presentation scheme that permits decay of these nonlinearities in order to minimize the error in estimation of NPT [Buckner, 1998]. However, nonlinearities also vary between brain areas and fixing parameters may add further errors to NPT estimation. We believe that the hemodynamic parameters not fixed have partially accounted for these spatial nonlinearities but their exact relationship to other parameters of the extended balloon model remains to be specified. Finally, it is important to note that the NPT is effectively the duration of the best on/off signal that models the neural activity as the input of a specific biophysical model and the interpretation of this parameter relies on strong assumptions about the mechanisms underlying the BOLD signal.

Given these caveats, we can draw some conclusions about the inferred NPT. The experimental paradigm of gender recognition of faces with emotion expressions as distracters activated FG, DACC, and bilateral DLPFC. Studies using conflict adaptation paradigms have suggested that these same areas form a neural network that ensures protection from distracters [Egner et al., 2007; Meriau et al., 2006]. We have predicted that the NPT would be similar to the duration of stimulus presentation in cortical areas where the stimulus is directly represented, regardless the experimental condition. In agreement with our expectation, the NPT in FG did not depend on the experimental condition and was equal to the stimulus presentation duration. The FG is a visual area specialized in face recognition and its activity is apparently not related to face expression processing [Kanwisher and Yovel, 2006].

The DACC is implicated in conflict monitoring while lateral prefrontal cortices are implicated in conflict resolution processes [Egner and Hirsch, 2005; Kerns et al., 2004]. In these regions, the duration of mental operations is probably variable and correlated with the NPT. Moreover, we expected the duration of these processes to be comparable to RT or, at least, significantly less than the stimulus presentation time. The estimated NPT in left DACC and right DLPFC for sad faces was in agreement with this expectation. Interestingly, Meriau et al. [2006] reported increased effective connectivity between these two areas during emotion decision making with face stimuli.

The estimated NPT for all areas in the control experimental condition of no concomitant emotional distracter was equal to stimulus presentation time. This finding can be interpreted as maintenance of neural activity in the neural network for the neutral faces stimuli, which should be tested by other experimental approaches. Finally, in agreement with the hypothesis of laterality in function of DLPFC for emotional processing [Wager et al., 2003], the estimated NPT was significantly shorter for sad faces than for neutral faces in right but not left DLPFC. The evidence of right dominance in DLPFC for negative emotions processing has led to a hypothesis of imbalance between right

and left DLPFC activity in major depression. According to this hypothesis there is a hyperactivity of right when compared with left DLPFC in depressed individuals [Grimm et al., 2007]. The application of the same experimental procedure to subjects with major depression will be used to test this imbalance hypothesis. Another perspective is to apply the NPT concept in the biophysical model underlying dynamic causal model (DCM).

In summary, we developed a more reliable method for estimation of neural activity duration from BOLD signal. This is a highly valuable measure for cognitive studies, specially adding information to classical behavioral data as response time.

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APPENDIX

The balloon model is an input-state-output dynamical system proposed by Buxton et al. [1998]. The input functions are the regional cerebral blood flow (f_{in}) and oxygen extraction rate (E); the outputs are a voxel's blood volume (v) and deoxyhemoglobin content (q). The functions expressed in lower case are normalized with respect to

TABLE IV. Parameters used in the BOLD model

Parameter	Value	Range	References
ε	1.0	0.5–1.5	[Friston et al., 2000]
τ_M	1.0	0.73–1.4	[Friston et al., 2000]; [Mandeville et al., 1999]
E_0	0.4	0.2–0.55	[Friston et al., 2000]
α	0.38	0.33–0.7	[Grubb et al., 1974]; [Mandeville et al., 1999]
τ	10.0	0–30.0	[Buxton et al., 2004]
V_0	0.03	0.01–0.04	[Buxton et al., 1998]
k_1	$7E_0$	—	[Buxton et al., 1998]; [Ogawa et al., 1993]
k_2	2	—	[Boxerman et al., 1995]; [Buxton et al., 1998]
k_3	$2E_0-0.2$	—	[Boxerman et al., 1995]; [Buxton et al., 1998]

The values of the parameters of the biophysical model used are shown in the second column. The third column represents the range of possible values for each parameter based on the literature and the fourth column presents the main works in which the parameters were estimated.

baseline values. The balloon model consists basically of the following system of differential equations:

$$\begin{cases} \frac{dv(t)}{dt} = \frac{1}{\tau_M} [f(t) - f_{\text{out}}(t)] \\ \frac{dq(t)}{dt} = \frac{1}{\tau_M} [E(t) f(t) - \frac{q(t)}{v(t)} f_{\text{out}}(t)] \end{cases}, \quad (\text{A1})$$

where τ_M is constant. The oxygen extraction rate $E(f, E_0)$ is defined as a nonlinear function of cerebral blood flow, based on an oxygen limitation model:

$$E(f, E_0) = \frac{1 - (1 - E_0)^{1/f(t)}}{E_0}, \quad (\text{A2})$$

where E_0 is a constant that represents the baseline rate of extraction of oxygen. The blood flow out of the voxel $f_{\text{out}}(t)$ is defined by an empirical law (first term of the equation, Grubb et al. [1974]) plus the derivative of cerebral blood volume with time [Buxton et al., 2004]:

$$f_{\text{out}} = v(t)^{1/\alpha} + \tau \frac{dv(t)}{dt}, \quad (\text{A3})$$

where τ and α are constants. The parameters of the dynamical system are the constants α , called Grubb's exponent, the time-constant for venous compartment filling τ_M , the time-constant for the viscoelastic effect τ and oxygen extraction rate at rest E_0 . The model is a system of two nonlinear first-order differential equations with no trivial analytical solution. For the purposes of the present work, the parameters were fixed, based on published experimental measures (Table IV). Solutions of the system of differential equations can be obtained numerically for any given input function $f(t)$.

From the output of the dynamical system it's possible to estimate the BOLD effect $y(t)$ using the nonlinear equation

$$y(t) = V_0 \left\{ k_1 [1 - q(t)] + k_2 \left[1 - \frac{q(t)}{v(t)} \right] + k_3 [1 - v(t)] \right\} \quad (\text{A4})$$

where k_1 , k_2 , and k_3 are constants that depend on machine characteristics and oxygen extraction rate at rest and V_0 is the blood volume of the voxel at rest. The values of these parameters are shown in Table IV. It has been shown that the nonlinear version of the equation for the BOLD effect (Eq. (A4)) performs better than the linear version in capturing signal variations [Stephan et al., 2007].