Examination of the Linearity of BOLD FMRI Responses in a Higher Level Cognitive System

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Introduction

Conventional methods of analyzing the FMRI time series are predicated on the assumption that the relationship between evoked neuronal activity and ensuing hemodynamic response can be approximated by a linear convolution using a fixed and time invariant hemodynamic response function [1]. These methods operate under the assumption that processes which give rise to the FMRI time series signal constitute a linear system [2]. Variations from linearity have been observed in the primary visual [3], auditory [4] and sensorimotor [5] cortices. One important manifestation of these nonlinear effects is a modulation (damping) of the hemodynamic response due to a given stimulus by preceeding stimuli which are proximate in time. This effect has been observed under high stimulus presentation rates (one word cue per second for auditory responses [5]).

We have sought to examine the linearity of the hemodynamic response in higher order cognitive systems, specifically the language areas of the medial frontal cortex. The hemodynamic response function (HRF), for a single event word generation task was estimated in a paradigm independent manner by using a deconvolution analysis. Using the knowledge of the single word HRF we examined the linearity of the hemodynamic response in the language system by varying the rates of word generation and comparing the observed responses with the calculated linear system responses.

The FMRI signal in a voxel can be expressed in terms of a convolution of the stimulus function with the impulse response function associated with the stimulus, $y(t) = S(t) \otimes H(t) + \varepsilon(t)$, where *S(t)* is the stimulus time series and *H(t)* is the HRF, $\varepsilon(t)$ is the gaussian noise and *y(t)* is the signal at a given voxel. Thus knowing the signal time series and the stimulus vector one can estimate the HRF by the deconvolution of *y(t)* and *S(t)*. Conversely we could use the estimated HRF for a single word generation stimulus to predict the linear system response by convolving the HRF with the stimulus function *S(t)*, obtained from the knowledge of the task.

Methods

Two normal control subjects performed a series of word generation tasks. In the first task subjects were asked to overtly generate words to category cues. The inter-stimulus interval between category cues was assigned to be 12, 15 or 18 sec in a pseudo-random manner. The subjects performed two 4 min functional runs of this task. The second task was a paced semantic word generation paradigm wherein the subjects were given a semantic category cue followed by 3 or 6 equally spaced helper cues in 15 sec and had to generate overtly one word for each secondary cue. The rest intervals between the 15 sec blocks of active durations were assigned to be 10.5, 12.0 and 15 sec in a pseudo-random manner. The subjects performed two 3 minute runs each for the three-word block task and the six-word block task.

Image Acquisition Images were obtained using a 1.5T GE Signa with a 2-spiral gradient echo scan with 10 contiguous sagittal or coronal 5.0 mm thick slices of the medial frontal cortex, 180 mm FOV, 128 x 128 matrix, TR/TE/FA = 750ms/40ms/50deg. Two functional runs were acquired with 150 images in each run, 1.5 sec per image for the single word generation task. Two functional runs were acquired with 120 images in each run, 1.5 sec per image for each of the two block word generation tasks.

Image Analysis For the single word generation task the two functional runs were concatenated to obtain a 300-image FMRI time series. The hemodynamic response was obtained at each voxel by deconvolving the FMRI time series with the the stimulus time series. The estimated response function for the event related task (EHRF) was then convolved with the stimulus vector to obtain a fitted signal time series. An F-test was performed to determine the goodness of fit of the fitted time series to the observed FMRI time series. The co-efficient of determination, R^2, was also evaluated to quantify the activation.

For each of the two blocked word generation tasks the two functional runs were concatenated to obtain a 240-image FMRI time series. The block paradigm hemodynamic response (BHRF) was obtained at each voxel by deconvolving the FMRI time series with the the stimulus time series (the time series of the injection of the semantic category cues). The estimated response function (HRF) was then convolved with the stimulus vector to obtain a fitted signal time series. An F-test was performed to determine the goodness of fit of the fitted time series to the observed FMRI time series. The coefficient of determination, R^2, was also evaluated to quantify the activation. The time series predicted by linear system analysis, for each of the two blocked word tasks, was obtained by convolving the single word estimated response (EHRF) with the time series of individual word generation in the corresponding block paradigm.

Results & Discussion

Figure 1 shows the estimated time locked signal changes for an 3-word activation block obtained through the two methods, linear convolution of the EHRF with the individual word time series and the method wherein each block is treated as an impulse. Figure 2 shows the same for the 6-word generation task. From the figures it can be seen that observed signal change is less than what is calculated from a linear sytem prediction. The damped (refractory) nature of the response increases with the rate of stimuli presentation. It must be noted that the refractory behaviour of the hemodynamic response occurs at much lower frequencies of stimuli presentation than is seen in primary sensory areas like auditory cortex,etc. This demonstrates the stronger nonlinear behaviour of word generation responses.

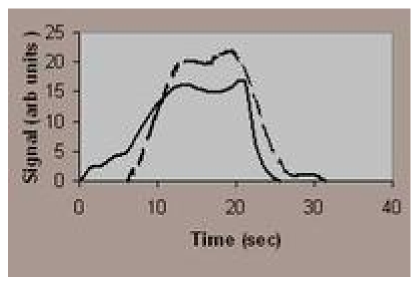

Fig 1: Estimated response calculated from the linear system model (dashed) and the observed response (solid) for a 3-word block stimulus.

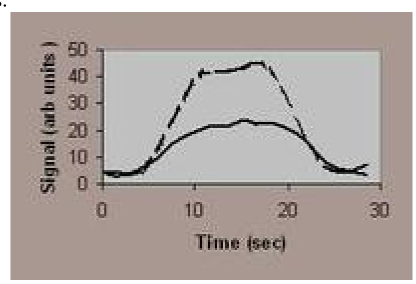

Fig 1: Estimated response calculated from the linear system model (dashed) and the observed response (solid) for a 6-word block stimulus.

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