Brain state classification of rapid event-related fMRI using mixed models

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INTRODUCTION Recently, there have been several examples of brain state classification with fMRI [1-3]. For block design data, each image can be represented as a vector with a corresponding class label based on the experimental paradigm. For event-related (ER) data, though, several images are required to represent the hemodynamic evolution of an evoked response, and for rapid ER designs these responses can overlap considerably. Thus, an appropriate vector representation for ER data is a critical consideration. Previous studies have generated "hyper-images" constructed by concatenating images within the hemodynamic response [1,4]. This approach essentially relies on the same principle as time-locked averaging, which has limited power to accurately estimate the hemodynamic response function (HRF). Another consideration is that hemodynamic responses are known to vary with repetitions of identical stimuli [5]. The goal of this study is to evaluate mixed models [6] to provide an epoch-by-epoch representation for ER brain state classification. In this study, we compare time-locked and mixed model hyper-image representations on simulated time series. We demonstrate the superiority of mixed models for accounting for between and within HRF variation and show that this translates to improved classification accuracy as measured by support vector classification (SVC) [7].

THEORY Under the assumption of linear time invariance, the BOLD signal *y[t]* (with time *t*=0,…,T-1) is modeled as the convolution of a neuronal response *x[t]* with a hemodynamic response *h[t]* plus noise *n[t]*. We approximate stimulus events in *x[t]* as a series of discrete delta functions filtered by an *h[t]*, having finite support of length, L. When multiple types of stimuli (s=1,…,S) are presented, their contributions are additive (Eqn. 1). The equivalent matrix representation is given in (Eqn. 2), where **y** and **n** are T×1 column vectors, *X* is a T×(LS) matrix, and **h** is (LS)×1. From **y**, *X*, and a sufficiently long estimate of L, it is possible to estimate **h** with ordinary least squares as in (Eqn. 3). If the interstimulus intervals are randomized, "selective averaging" (with stimulus-time-locked windows of length L) will also provide an estimate of **h**.

$$y[t] = \sum_{s=1}^{S}(x_s[t] * h_s[t]) + n[t] \quad (1)$$

$$\mathbf{y} = X\mathbf{h} + \mathbf{n} \quad (2)$$

$$\mathbf{h} = (X^T X)^{-1} X^T \mathbf{y} \quad (3)$$

$$\mathbf{y} = X\mathbf{h} + V\mathbf{g} + \mathbf{n} \quad (4)$$

For classification, we do not estimate the average $h_s[t]$, *per se*, but require multiple observations of the responses to each of the S stimuli. To estimate the HRFs for each trial, we rewrite Eqn. 2 to obtain the mixed model in Eqn. 4. where *V* is N×(TL) and contains the information of *X*, and **g** is (TL)×1 and is the vector of random effects. The basic idea is to estimate each **h** by accounting for the additive effects of other event responses.

METHODS Simulations were performed in Matlab (MathWorks, Natick, MA). The function, mixed.m [8], was used to solve all mixed model equations.

<u>Simulation 1 (estimating two HRFs from a time series):</u> Time series were simulated using a sampling rate (TR) of 500 ms and length of 500 samples, approximating a 4 min. run. Two HRFs ($\mathbf{h}_1$ and $\mathbf{h}_2$) were generated using uniform distributions for the following parameters: delay { $\mathbf{h}_1$=[1,3], $\mathbf{h}_2$=[0,1] samples}, width { $\mathbf{h}_1$=[10, 14], $\mathbf{h}_2$=[14, 16] samples }, amplitude { $\mathbf{h}_1$=[1.4,1.7], $\mathbf{h}_2$=[0.5, 0.8] }, added baseline { $\mathbf{h}_1$=0.0, $\mathbf{h}_2$=0.0 }. Noise was added ($\mathbf{n}$~N(0,0.25)), and there were 40 onset times for both HRFs, distributed across the first 480 samples, allowing responses to return to baseline at the end of the experiment.

<u>Simulation 2 (classification in a voxel preferentially selective to one stimulus):</u> Parameters: 720 samples, delay { $\mathbf{h}_1$=[1,3], $\mathbf{h}_2$=[0,2] samples}, width { $\mathbf{h}_1$=[10, 14], $\mathbf{h}_2$=[14, 16] samples }, amplitude { $\mathbf{h}_1$=[1.3,1.7], $\mathbf{h}_2$=[0.2, 0.3] }, added baseline { $\mathbf{h}_1$=-0.5, $\mathbf{h}_2$=-0.5 }.There were 72 onset times for both HRFs, distributed across the first 700 samples, allowing responses to return to baseline at the end of the experiment. Noise had variances ranging from 0.36 to 100, with 60 time course realizations per noise level. Two time courses were generated at a time, and, as described in other studies [2], both were resampled to alternately serve as train and test data (providing 60 total classification accuracy estimates per noise level). Classification was performed using time-locked and mixed model representations using SVC (linear kernel, parameter C = 1.00, $\mathbf{h}_1$ = class +1, $\mathbf{h}_2$ = class -1), under the assumption that the stimulus class labels are known in training data, but for testing data the class labels must be estimated assuming only knowledge of the neuronal response times.

RESULTS Fig. 1 shows results for Simulation 1, and Fig. 2 shows results for Simulation 2.

DISCUSSION AND CONCLUSION We have demonstrated a mixed model approach that accounts for two sources of variation in ER-data: between HRF variation from a voxel's relative sensitivity to different stimulus types and within HRF variation to explain the heterogeneity of a voxel's response to several repetitions of the same stimulus. Beyond the general utility of this approach for obtaining better estimates of **h** than those obtained by Eqn. 3, it also enabled us to generate improved hyperimages suitable for vector-based classification algorithms. Simulation 1 demonstrates a pixel with a different HRF for two classes of stimuli. Simulation 2 treated a pixel that was essentially sensitive to only one stimulus, and thus should be easy to classify. Even under low noise conditions, though, the time-locked representation has a significant error rate. Under extreme SNR conditions, the mixed model is still superior (on average) but shows increased variability. It is expected that the combination of mixed modeling representation with voxel selection techniques [4] will provide a comprehensive framework for brain state estimation for event-related studies.

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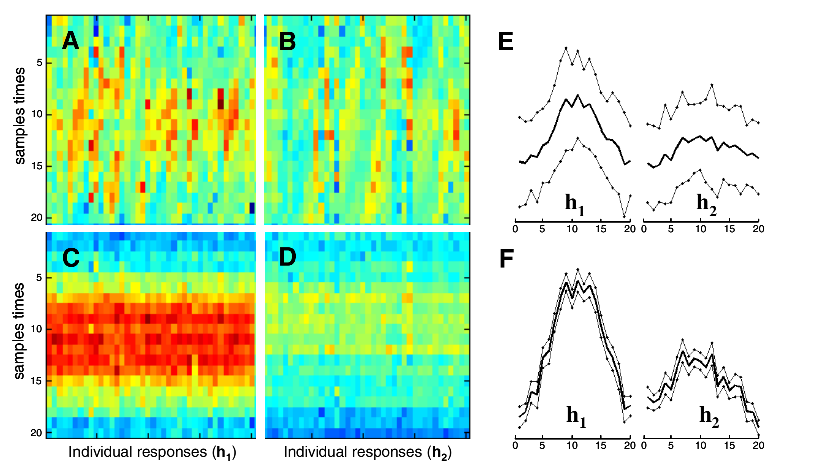

Figure 1 (Simulation 1): Images A and B show time-locked representations of the 40 $\mathbf{h}_1$ and $\mathbf{h}_2$ realizations, respectively. Images C and D show the corresponding mixed model representations. Plots E and F show the corresponding HRF estimates that would come from averaging the columns of A-D (mean +/- std). Note that F shows better estimates of $\mathbf{h}_1$ and $\mathbf{h}_2$.

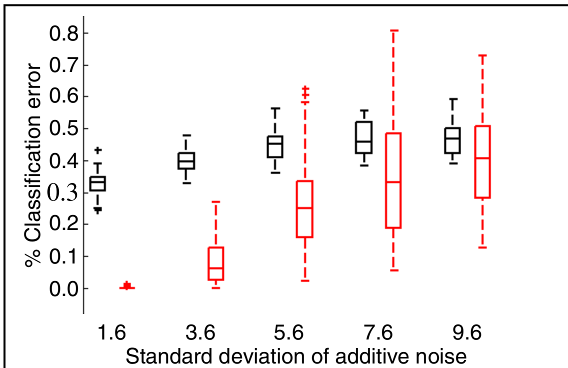

Figure 2 (Simulation 2): Boxplot of % SVC error vs. noise level, generated from 60 estimates per noise level. Time-locked results are black, and mixed model results are red. Note that red has better accuracy.